International
RECORD OF MEDICINE
A Journal of Advanced Experimental and Clinical Reports

Originally Published as American Medical Intelligencer. Founded Philadelphia, 1837

WHOLE NUMBER 2817

VOL. 164 NO. 3 MARCH 1951

THE EFFECT OF ORAL ADMINISTRATION OF CERTAIN STREPTOMYCES FERMENTATION PRODUCTS ON "HEMOLYTIC" ANEMIAS WITH NOTES ON CERTAIN SIMILARITIES BETWEEN THE EFFECTS OF INTESTINAL FLORA REVERSION AND THOSE OF ADRENOCORTICOTHERAPY
Robert D. Barnard

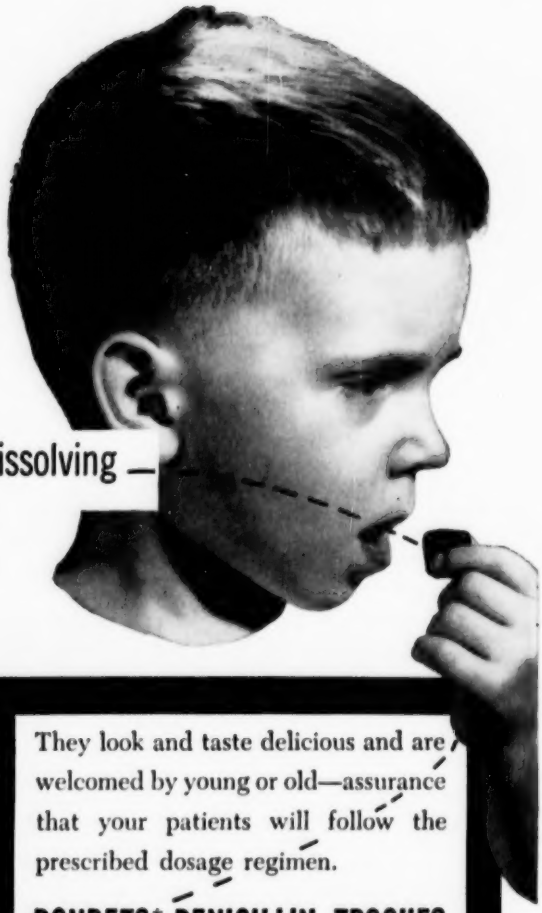
CHRONIC INFECTION AND THE NON-SPECIFIC REACTION
Howard B. Emerson, Jr.

CARCINOGENESIS IN THE LIGHT OF THE TROPHOBLASTIC OR UNITARIAN THESIS OF CANCER
Ernst T. Krebs, Jr.

VOL. 8 NO. 3 MARCH 1951

GENERAL PRACTICE CLINICS
A Publication of
THE WASHINGTON INSTITUTE OF MEDICINE

20,000 units of penicillin in a slowly-dissolving — hard candy base



One Pondet provides high local penicillin levels lasting a half-hour

They look and taste delicious and are welcomed by young or old—assurance that your patients will follow the prescribed dosage regimen.

PONDETS* PENICILLIN TROCHES

For local treatment and prophylaxis of oral infections caused by penicillin-sensitive organisms.

*Trade Mark

Wyeth Incorporated, Philadelphia, Pa. Wyeth

International

RECORD OF MEDICINE

A Journal of Advanced Experimental and Clinical Reports

Originally Published as American Medical Intelligencer. **Founded Philadelphia, 1837**

WHOLE NUMBER 2817

VOL. 164 NO. 3 MARCH 1951

Published Monthly by

THE WASHINGTON INSTITUTE OF MEDICINE

1708 MASSACHUSETTS AVE., N.W., WASHINGTON 6, D. C.

Editorial Offices
19½ East 62nd Street, New York 21, N. Y.

Advertising Department
667 Madison Avenue, New York 21, N. Y.

A cumulative cross reference index is included in the final issue of each volume. Subscription rate: 1 year, $7.50; 3 years, $15.00. Copyright 1951 by Washington Institute of Medicine. Entered as second class matter at Washington, D. C. and Lancaster, Pa. under the Act of March 3, 1879. Printed in U. S. A.

GENERAL PRACTICE CLINICS

VOL. 8 NO. 3 MARCH 1951

EDITORIAL BOARD

Félix Martí Ibáñez, M.D., *International Editor*

Fred L. Adair, M.D.
University of Chicago

Roma Amyot, M.D.
Editor-in-Chief, L'Union Medicale du Canada

Harry L. Arnold, Jr., M.D.
Editor, Hawaii Medical Journal
Honolulu, Hawaii

W. Wayne Babcock, M.D.
Temple University

Howard C. Ballenger, M.D.
Northwestern University

Alexander W. Blain, M.D.
Wayne University

Alfred Blalock, M.D.
Johns Hopkins University

W. F. Braasch, M.D.
Mayo Clinic

J. Mackenzie Brown, M.D.
University of Southern California

Leroy A. Calkins, M.D.
University of Kansas

Bayard Carter, M.D.
Duke University

Russel L. Cecil, M.D.
Cornell University

George Morris Coates, M.D.
University of Pennsylvania

Frederick A. Coller, M.D.
University of Michigan

Willard R. Cooke, M.D.
University of Texas

Walter T. Dannreuther, M.D.
New York University

Clyde L. Deming, M.D.
Yale University School of Medicine

R. S. Dinsmore, M.D.
Cleveland Clinic

Daniel C. Elkin, M.D.
Emory University

Ludwig A. Emge, M.D.
Stanford University

Harold K. Faber, M.D.
Stanford University Hospital

Joseph H. Fobes, M.D.
New York Medical College

Willis D. Gatch, M.D.
University of Indiana

Louis J. Gelber, M.D.
Rockville Center, L. I., N. Y.

N. C. Gilbert, M.D.
Northwestern University

Bernard J. Hanley, M.D.
University of Southern California

French K. Hansel, M.D.
Washington University

Clyde A. Heatly, M.D.
University of Rochester

Henry F. Helmholz, M.D.
Mayo Clinic

Frank Hinman, M.D.
University of California

Paul H. Holinger, M.D.
University of Illinois

Clarence B. Ingraham, M.D.
University of Colorado

Chevalier L. Jackson, M.D.
Temple University

J. Bay Jacobs, M.D.
Georgetown University

Marvin F. Jones, M.D.
New York, N. Y.

Robert W. Keeton, M.D.
University of Illinois

Harry H. Kerr, M.D.
George Washington University

William J. Kerr, M.D.
University of California

I. Newton Kugelmass, M.D.
New York, N. Y.

Carl H. Lenhart, M.D.
Western Reserve University

Dean M. Lierle, M.D.
University of Iowa

Ralph H. Major, M.D.
University of Kansas

Roy D. McClure, M.D.
Henry Ford Hospital

Irvine McQuarrie, M.D.
University of Minnesota

Alton Ochsner, M.D.
Tulane University

Thomas G. Orr, M.D.
University of Kansas

Henry Boylan Orton, M.D.
New York Polyclinic

Winfred Overholser, M.D.
George Washington University

James E. Paullin, M.D.
Emory University

Franklin L. Payne, M.D.
University of Pennsylvania

Louis E. Phaneuf, M.D.
Tufts College Med. School

E. D. Plass, M.D.
University of Iowa

Tracy J. Putnam
Columbia University

Fred W. Rankin, M.D.
Lexington, Ky.

B. O. Raulston, M.D.
University of Southern California

Lyman G. Richards, M. D.
Harvard University

Leonard G. Rowntree, M.D.
Miami, Fla.

Raymond Sackler, M.D.
New York, N. Y.

Lewis C. Scheffey, M.D.
Jefferson Medical College

Edward A. Schumann, M.D.
Philadelphia, Pa.

Cyrus C. Sturgis, M.D.
University of Michigan

Herbert Thoms, M.D.
Yale University

Paul Titus, M.D.
Pittsburgh, Pa.

Donald V. Trueblood, M.D.
Seattle, Wash.

Norris W. Vaux, M.D.
Jefferson Medical College

Theodore E. Walsh, M.D.
Washington University

Owen H. Wangensteen, M.D.
University of Minnesota

James J. Waring, M.D.
University of Colorado

John C. Whitehorn, M.D.
Johns Hopkins University

Karl M. Wilson, M.D.
University of Rochester

Fred W. Wittich, M.D.
Minneapolis, Minn.

INTERNATIONAL RECORD OF MEDICINE

and

GENERAL PRACTICE CLINICS

March CONTENTS 1951

INTERNATIONAL RECORD OF MEDICINE

The Effect of Oral Administration of Certain Streptomyces Fermentation Products on "Hemolytic" Anemias with Notes on Certain Similarities Between the Effects of Intestinal Flora Reversion and Those of Adrenocorticotherapy
Robert D. Barnard 117

Chronic Infection and the Non-Specific Reaction
Howard B. Emerson, Jr. 130

Carcinogenesis in the Light of the Trophoblastic or Unitarian Thesis of Cancer. Part I.
Ernest T. Krebs, Jr. 141

GENERAL PRACTICE CLINICS

Obstruction of the Lower Portion of the Urinary Tract in Infants and Children 170

Diverticula of the Female Urethra 170

The Female Urethra: A Histologic Study as an Aid in Urethral Surgery 171

Memory Studies in Electric Convulsion Therapy 172

Suicide 173

Investigation of Autonomic Responses in Psychopathic Personalities 173

Book Reviews

The Merck Manual of Diagnosis and Therapy 174

Textbook of Endocrinology 174

Therapeutics in Internal Medicine 175

Manual of Allergy for the Patient 175

ALHYDROX ADSORBED DIP-PERT-TET†
BUILDS MAXIMUM... DURABLE IMMUNITY

Alhydrox Increases Dip-Pert-Tet Antigenicity—In actual usage as well as reported clinical studies it has been shown that Dip-Pert-Tet Alhydrox produces uniformly superior levels of serum antitoxins. [1, 2, 3]

Alhydrox Reduces Dip-Pert-Tet Reaction Frequency—Prove it to yourself, Doctor . . . vaccinate 25 patients with a plain or alum precipitated combination and another 25 patients with Cutter Dip-Pert-Tet Alhydrox. You will see for yourself that there is a minimum of local reactions with Alhydrox adsorbed Dip-Pert-Tet.

Depend On Dip-Pert-Tet Alhydrox—for simultaneous immunization against Diphtheria, Pertussis, Tetanus. High pertussis count – each cc. contains 30,000 million Phase 1, H. pertussis organisms.

Insist on CUTTER
DIP-PERT-TET ALHYDROX
A FIRST NAME IN COMBINED TOXOIDS

*Cutter Trade Name. †Dip-Pert-Tet Alhydrox—Purified Diphtheria and Tetanus Toxoids and Pertussis Vaccine combined, Aluminum Hydroxide adsorbed.

1. Miller, J. J., Jr., and Ryan, Mary Louise. The Duration of Serologic Immunity. Pediatrics 1:8, Jan., 1948.
2. Lapin, Joseph L., Combined Immunizations. Advances in Pediatrics, Vol. IV. Interscience Publishers, Inc., New York, 1949.
3. Costello, Cyril, Improved Methods in Combatting Tetanus. J. Missouri M. A., 46:582, Aug., 1949.

CUTTER LABORATORIES • BERKELEY, CALIFORNIA

Producers of famous purified Dip-Pert-Tet Plain, a product of choice for immunizing older children and adults.

International

RECORD OF MEDICINE

WHOLE NUMBER 2817

VOL. 164 NO. 3 MARCH 1951

The Effect of Oral Administration of Certain Streptomyces Fermentation Products on "Hemolytic" Anemias with Notes on Certain Similarities Between the Effects of Intestinal Flora Reversion and Those of Adrenocorticotherapy

ROBERT D. BARNARD, M.D., New York, N. Y.

Concentrates from the by-products of streptomyces fermentation processes which had been designed for the production of antibiotics (streptomycin, aureomycin and terramycin) were found to have marked growth-promoting properties in poultry, hogs and fur-bearing animals.[1] This was attributed to their "B_{12}" content and the material has been commercially available as a feed supplement for almost two years. The writer's experimental work with this material in humans has also been of this duration though it was recognized early that the effects in humans were of an entirely different nature than those produced either by oral or parenteral B_{12} administration.[2] Test subjects have now included about 500 patients with a variety of disorders, all of whom have been given either dried, crude spent broth from streptomyces griseus fermentation, concentrates from non-antibiotic producing streptomyces strains and antibiotics derived from s. griseus, s. aureofaciens or s. rimosus (streptomycin, aureomycin and terramycin respectively). All of these materials have therapeutic effects which may be qualitatively but not quantitatively similar to those of adrenal cortex extracts. This might be understandable for the crude extracts which contain steroid material. However, the same effect, though varying among patients, is noticeable on the oral administration of the gram-negative bacillary suppressor antibiotics. Thus, in antihistamine-resistant allergies, the response to doses of s. griseus broth, containing very small amounts of antibiotic, are frequently rapid and accompanied, as are those with adrenal cortex extracts, by a fall in circulating eosinophiles, an amelioration of the symptoms of the allergy and a tendency to sodium and water retention which has precipitated congestive failure in some patients with poor cardiac reserve.

For over a year, while employing the same s. griseus residue sold as

"animal protein factor" in humans, we were unaware as to the reasons for its virtues (other than to be certain that B_{12} alone was not concerned). And these virtues were quite evident even to skeptical observers. The growth effects, reported for crystallin B_{12} in retarded children as well as the disappearance of allergic conditions, reported by another investigator[3] while our own study was in progress, can be emphatically confirmed. Patients with rheumatoid arthritis, in significant numbers, though by no means the majority of such patients, gave objective and subjective evidence of relief so rapidly after institution of a daily oral dose of dried s. griseus broth, that the results would be termed "dramatic" had that word, in its clinical sense, not already been copyrighted by the advocates of corticotherapy.[4] It was of particular interest that therapeutic effects were most prominent in those whose ailments were of the "atopic" or "intrinsic hypersensitivity" nature. Reports of results in selected patients with atopic dermatoses, demyelinating neuropathies, rheumatoid conditions and serious blood dyscrasias have been rendered.[5, 6]

It was in patients of the last category that the probable effect of s. griseus broth, as due to its residual antibiotic content, was uncovered. This residual antibacterial activity had been assayed as streptomycin (on the basis of E. coli suppression) and its content considered to be streptomycin in a concentration of 300 gammas/gram. This meant that our patients were getting, in some instances, as little as one milligram per day of an antibiotic that could not leave the intestinal tract since soluble streptomycin salts are inabsorbable from the gut.[7] Finally, the fact emerged that those patients in whom a therapeutic effect was forthcoming from this administration had sustained coincidentally, a change in the bacterial content of the stool, the coliform and aerogenes groups all but disappearing to be replaced by gram positive organisms (lactobacilli and s. fecalis). However, the most important lesson gleaned from perusal of the acute leukemia cases was that this material, or its antibiotic content, was a very powerful hematinic. Acute leukemic patients frequently maintained active erythropoiesis and transfusion could be foregone entirely. Three cases of myelaplasia following x-irradiation, resumed erythropoiesis, one on the administration of s. griseus broth, one on oral administration of 50 milligrams of streptomycin sulfate and the third on being started on a course of aureomycin. Three infants with megaloblastic anemia responded in one instance to s. griseus residue, in another to chloromycetin (the antibiotic produced by streptomyces venezueliensis) and in a third to terramycin. In the last case, the stool showed streptococcus faecalis almost exclusively during the remissive phase; an interesting commentary on the elaborate theories worked out for the folic acid requirement of these organisms.[8] Suggestive responses have also been forthcoming in the anemias of infection, malignancy and glomerulonephritis and it has become increasingly apparent that the primary hematinic effects of streptomyces residues or the antibiotics derived from them were worthy of direct exploitation.

They were consequently applied to the treatment of acquired "hemolytic" anemia which is a secondary anemia of more frequent occurrence than commonly appreciated. Though the term, "hemolytic," is not academically sound, this anemia being due to an arrest of erythropoiesis in the erythroblastic or normoblastic stage (rather than to accelerated erythrocyte destruction as is usually stated), it is easily recognized by its association with gastro-intestinal disease or malfunction, by the presence of a circulating pseudoagglutinin which appears to be of a glycoprotein nature,[2] the poor response to transfusion which is frequently accompanied by reaction and notorious resistance to all previous modes of hematinic therapy. It appears likely that "hemolytic" anemias represent the most benign type of myelosuppressive dyscrasia and form the first member of the category in which we find addisonian anemia and the acute leukemias. The former represents marrow arrest in the megaloblastic stage while the latter is an expression of leukoblastic arrest. In fact, hemolytic "components" are invariably present to some degree in the more malignant dyscrasias of the category, viz., acholuric jaundice and urobilinuria are common to all and circulating antibodies are frequently demonstrable. The last appear in high concentration particularly in acute leukemics who have been transfused too liberally or frequently and (as in "hemolytic" anemia) are the covert cause of death through transfusion reaction. Addisonian anemia and that of acute leukemia, may be forms of "complicated, hemolytic" anemia. The five cases presented, all under hospital supervision, are of the "uncomplicated" variety; they were attended by no other manifest blood dyscrasia and their response to intestinal flora therapy is instructive.

In this report, comments applicable to a single case will be placed at the end of that case.

Case 1 (service of Dr. Max Schwartz)

A 53-year-old housewife complained of progressive weakness and palpitations over the past two months. Two years prior to the present admission (13 Jan. 50) she had had an episode consisting of loss of consciousness, rousing with mild disorientation and neurologic findings which were deemed to indicate a cerebral venous thrombosis. This responded to dicumerol therapy and she had been well until the onset of the present illness. Physical examination revealed a moderately obese patient with myxedematous facies, mild skin edema and minimal scleral icterus. The basal metabolic rate was plus 7. There were no neurologic sequelae to the last illness and except for a large, smooth uterine fundal mass, the physical examination was essentially negative. Blood examination showed an erythrocyte count of 3.3 millions, a hemoglobin of 63 decimillimolar and a hematocrit of .32. There were 5.2 thousand leucocytes per cu. mm. of which 62% were granulocytes without evident shift and the platelets, though there were many of the "fleshy" variety, were unclumped and of

normal number. There was marked erythrocytic anisocytosis, poikilocytosis and polychromatophilia and an occasional normoblast. The icterus index was 16, with indirect positive van den Bergh and the urinary urobilin was positive in a 1–200 dilution. In spite of the absence of thrombopenia and neutropenia, a diagnosis of addisonian anemia was entertained but the gastric juice without histamine impellation showed a *p*H of 3. Pending more exhaustive study (since it was now thought that there might be a gastro-intestinal malignancy) it was decided to transfuse the patient. A discrepancy between the results of the Rh tube test (where the patient's erythrocytes suspended in saline failed to agglutinate) and the slide test (where Rh positivity was indicated) led to further blood evaluation. A blocking antibody was apparently present since conglutination took place in bovine albumin and the Coombs test was strongly positive, leading to a diagnosis of hemolytic anemia. Transfusion was foregone and the radiologic gastro-intestinal study showing nothing of significance, it was decided to prepare the patient nutritionally for a future hysterectomy. She was discharged with instructions to take 5 grams of streptomycin broth concentrate containing 6 gammas of "B_{12}" (assayed as l. leichmanii factor) and 300 gammas of antibiotic (assayed as, but not known to be streptomycin) per gram, four times daily. On the occasion of the next visit, one week after discharge, the patient's appearance had definitely altered. The face had lost the puffy appearance, the skin was pink and moist and she had ceased to have palpitations. No nucleated erythrocytes could be found in the stained film. She was instructed to continue the oral supplement along with her regular diet and to report to the hospital in three weeks for admission for hysterectomy. When so reporting, the entirely normal hematologic and physical findings except for the uterine mass which had not changed, was so evident and since there were no complaints of inconvenience from the fibroid, she was allowed to retain the latter and dismissed without operation. She has been in good health since.

It is possible that this patient's "cerebral vascular accident" of 1948 was due to erythrocytic pseudoagglutination[10] ("sludging"); this phenomenon being common where blocking antibodies are extant. These antibodies appear to be glycoprotein in nature and it was conjectured that they may have arisen in this case from a degenerating fibroid. However, in most instances there must be some other origin for the sensitizing agent and the gastro-intestinal tract should always be under suspicion as the next case illustrates.

Case 2 (service of Dr. Arthur Feder)

A 63-year-old housewife of Teutonic extraction began to complain of bloating after meals, pyrosis, dyspnea and palpitation late in 1949. The past history was irrelevant and examination revealed only a "severe anemia" for which the usual polyvalent hematinics and vitamin mixtures were prescribed without avail. She was admitted to the hospital on 19 April 1950 for transfusion. During the attempt to cross match a com-

patible donation unit, an anomalous agglutination of the patient's unwashed erythrocytes led to further examination. The Coombs test was strongly positive as were the albumin and globin fortification tests. The icterus index was 12 and the plasma polyphenols, 6.6 milligrams per cent. The hematocrit was .21. There were 1.8 million erythrocytes, many of which were nucleated. Howell-Jolly bodies could be found in each field. Sternal aspirate showed a marked erythroid hyperplasia with a large number of erythroblastic rosettes and polynucleated normoblasts. Transfusion of washed erythrocytes was advised but whole blood was given, with the anticipated reaction which was, however, not severe. Immediately following transfusion the hematocrit was .25 but this fell to .22 twenty-four hours later. The patient was discharged on 21 April, unimproved and instructed to take 2½ grams of streptomycin broth (similar to but 1¼ times as concentrated as that used in Case 1) three times daily. Within three days of beginning treatment, the patient reported marked improvement in both gastro-intestinal and general symptoms but no further blood studies were made for six weeks while she continued on this regime. On 8 June there were no symptomatic residues, there were continuations of normal daily bowel movements and the hematologic status was a normal one with a hematocrit of .38, 4.3 million erythrocytes none of which were nucleated, and a negative Coombs test.

While this patient was being treated, contemporaneous studies had indicated the inpotency of concentrates from non-antibiotic producing strains of streptomyces in the induction and maintenance of clinical remission in acute leukemia.[5] These studies had also suggested the possible determinant role of coliform suppressor antibiotics in the therapy of the estrapenic dyscrasias. On the basis of assay figures, this patient could not have been obtaining more than 2500 antibiotic units (in terms of streptomycin but not necessarily that antibiotic since the latter is usually assayed for coliform suppression). Still, when it is considered that less than 1 gamma of streptomycin per gram of medium will suffice for complete coliform suppression, it is evident that sufficient antibiotic may have been continuously extant in the intestinal tract to effect a change in flora. It is likely that customary doses of 40 to 80 grams of streptomycin fermentation concentrate used in other patients[6] may have been much higher than necessary provided coliform suppression has been the determinant in these cases. Further evidence of such determinance is afforded by the third case presented.

Case 3 (service of Dr. Harold Goldberger)

A 32-year-old housewife of Irish extraction suffered from "constipation" and vague abdominal complaints prior and subsequent to an appendectomy four years ago. The operation made no change in her symptoms and she has secured bowel movements only by the daily taking of an emodin bearing cathartic. She had been nervous, irritable and pallid for

some weeks prior to admission for observation. General physical examination on 14 May was essentially negative. Laboratory examination elicited a pronounced indicanuria. The erythrocyte count was 3.8 million, hematocrit .35, and hemoglobin 64 decimillimolar. There were 4.6 thousand leucocytes of which only 32% were granulocytes. Stained smear also revealed a moderate thrombocytopenia and from 3–5 mature "normoblasts" per field. The plasma hemoglobin was 300 mgm.%; plasma thromboplastin was increased as denoted by rapid filar fibrin formation in the citrated sample. The plasma polyphenols were 4.9 mgm.%, the Van den Bergh positive in the indirect phase and the Coombs test, strongly positive. Because of overt plasma hemolysis, fragility test (which we disregard in any event) was not performed.

Cathartic medication, as well as the proprietary oral B_{12}, folic acid, iron combination which the patient had been receiving for some weeks, were discontinued. Terramycin, 1 gram daily in four divided doses along with a glassful of milk fortified with 20 grams of lactose was started on 16 May. On 18 May, there were two spontaneous, odorless bowel movements showing a predominantly gram positive bacillary content. Both lactobacilli and an endosporic clostridium were identified. On 19 May, three days after initiation of therapy, all "normoblasts" had disappeared and the peripheral smear was adjudged normal. The Coombs test was negative. Therapy was continued as above except for reduction of terramycin dosage to a single 250 mgm. capsule daily. After one week, the patient, though now in excellent health, stated that her appetite was becoming voracious, she had gained six pounds and did not want to become unstylish. The terramycin was discontinued on 26 May, milk-lactose being continued. Clinical relapse, with return of constipation and pallor, occurred within two weeks when it was noticed that the stools had a predominantly gram negative bacillary character. A second clinical remission was instituted with 50 mgm. of terramycin, four times daily. Ten days after institution of the last course of terramycin therapy, an intractable mucoid diarrhea developed and persisted for three weeks after discontinuance of terramycin. During the last period, a lactobacillus stool persisted. The diarrhea was finally brought under control by a high protein diet with a reversion to a proteolytic flora.

The foregoing case, beside its intended illustration of rapid hematinic effect of an antibiotic, also illustrates one of the difficulties encountered with such therapy. Severe, often intractable diarrhea after oral antibiotic therapy with evidence of mucoid colitis, has been studied in four patients. Incidentally, three of the latter were achlorhydric subjects but the condition did not yield to hydrochloric acid administration. Whether the mucus represents an allergic reaction to the antibiotic or one of its disintegration products, or to the type of intestinal flora which it induces, is unknown, though the persistence of the diarrhea long past the point of antibiotic therapy interruption would seem to indicate the latter possi-

bility. It may be that some patients are intolerant of anything but the usual proteolytic intestinal flora.

The next case, one of anemia associated with glomerulonephritis, is incorporated because of its interesting features aside from the fact that Emerson's recent studies[12] on the nature of this anemia (though he, himself, expressed no such opinion) indicates for it, the same type of marrow arrest seen in the previously presented cases.

Case 4 (service of Dr. Jac Gillman)

I. G., a 20-year-old factory worker was first admitted to the hospital in February, 1948, with fever, vomiting and a weeping dermatitis of the left forearm where it had been in contact with luminous paint with which she had been employed. The blood showed a moderate lymphosis but no anemia. The urine was negative. Over the past two years, the recurrent dermatosis became generalized and symmetricallized and anemia and glomerulonephritis developed. There have been 8 hospital admissions over this period, chiefly for generalization of the dermatosis, which has an atopic character; it invariably yielded to adrenal cortex extracts in an average period of 11 days. During the past year, she had received intensive parenteral B_{12} therapy in an effort to control the anemia which, on the last hospital admission (22 July 50) for recurrence of dermatosis and vomiting, showed 2.09 million erythrocytes with a color index of 1.1. Terramycin, 50 milligrams four times daily with milk was begun on 23 July. By the next day, the weeping dermatosis had begun to abate and had entirely cleared by 26 July. The erythrocyte count at this time was 3.2 million with a color index of 1.0. The regime was continued, with a liberalization of diet. On 3 August, there were 3.7 million erythrocytes with a color index of 0.8 and albumin had diminished to 2 plus; the urinary statuses and blood picture on the date of discharge being better than at any time in the past 18 months.

Previous close observation on this patient, in whose case incidentally the response to adrenal cortex extract had been adduced as evidence before the industrial commission of the atopic nature of her systemic and dermatologic conditions, had enabled us to "standardize" her on adrenal cortex extract, i.e., it was known that between one and two weeks of parenteral administration of the lipo-extract was necessary to improve the dermatosis. Terramycin therapy required a comparable four days and the recovery was more complete. It may be legitimate to assume, as was done in the case of adrenal cortex response, that rapid response to low antibiotic dosage might also designate the responding process as an atopic one.[13]

Case 5 (writer's service)

A 47-year-old housewife who still menstruated regularly had what appeared to be a "viral" pneumonia in May, 1950. For this, terramycin in 1.5 gram daily dosage led to sufficient improvement in four days to

enable the patient to do her housework. However, a moderate cough and afternoon rise in temperature of about a degree, led to a re-evaluation on 6 July. Routine blood study showed a moderate benign systemic lymphosis (so called "chronic infectious mononucleosis"), an erythrocyte count of 3.6 millions with a color index of 1.1. Free hydrochloric acid was found in the test meal and aside from a 1 plus cephalin flocculation test, the remainder of the examination was negative. It had been our previous practice to treat such cases with oral adrenal cortex extract, as advocated by Isaacs,[14] but in this instance, intestinal flora reversion therapy with 50 mgm. of terramycin, bidaily, was instituted instead. Following the third dose, there was a shaking chill and the temperature rose to 102.2. The patient refused additional terramycin. She appeared so pallid that, on clinical grounds a malignant hematologic dyscrasia was seriously considered but the patient refused sternal aspiration and insisted on discharge. Since she was afebrile on 8 July, this was permitted. By 29 July, the blood picture had deteriorated, the erythrocytes numbering 3.1 with a color index of 1.2, and persistence of monocytoid lymphocytes. The patient exhibited many fresh subcutaneous nodules over the scalp and phalanges which were adjudged to be rheumatic. She was instructed to take a single 750 mgm. tablet of s. griseus extract before retiring, along with a glassful of milk, as a "tonic." The results were quite gratifying. The patient reported back voluntarily two days after starting the new medication. The pallor had entirely disappeared as had the scalp nodules. At the end of two weeks the erythrocyte count had risen to 3.9 millions with a reversion to normochromia and the patient stated that she had not felt so well in years.

The last case represented what was presumably an anemia associated with rheumatoid diathesis. This type of anemia is analogous to the "hemolytic" variety in that an erythroblastic arrest is frequently demonstrated; though no marrow examination was done, it may be assumed that the initial macrocytosis of the last patient indicated such an arrest. It is now stated that the anemia of arthritis responds to corticotherapy along with the other manifestations of rheumatoid disease and since (from other cases) it is known that this syndrome is also amenable to streptomyces derived antibiotic therapy, another similarity between the latter and corticotherapy is uncovered.

General Discussion

Davis[15] has ascribed marrow arrest in some anemias to the effects of acetylcholine which he considers to be a marrow vasodilator and to permit such reoxygenation of the bone marrow that there is no call for erythropoiesis. While agreeing with Davis that certain cholinergics are capable of erythropoietic suppression, the writer considers this effect to be due to a hypersensitivity reaction on the part of the marrow.[16] In the human, normoblastic proliferation is essential for normal blood cholinesterase production and the latter is essential, in turn for the neutralization of chol-

inergies which are constantly being elaborated elsewhere in the body. While Davis stresses the role of acetylcholine as a marrow suppressor, peptones, which are also ubiquitous intermediaries in metabolism are more likely to be incriminated.[17] In addition to those peptones which arise during protein catabolism, there appears to be a supply from the intestinal tract containing a proteolytic flora. Indeed Vaughn,[18] many years ago held these to be the toxic factors in "autointoxication" as opposed to Metchnikoff's idea that smaller degradation products were responsible.[19] Barnard reached the conclusion, on theoretic grounds, that cholinergics could summate, whatever their source and that if they reached a certain liminal concentration, would precipitate hypersensitivity phenomena whose character would depend on the "atopic" reactivity of the individual.[20]

Certain "refractory" anemias are undoubtedly in this category and it is curious to review the suggestive association between such anemias and gastro-intestinal malfunction as well as their response to modification of that tract. These statements were frequent at a time when marrow aspiration was an unusual procedure and no distinction was made between the various stages of erythropoietic arrest. Thus Metchnikoff insisted that such anemias not infrequently yielded to implantation of a lactobacillus flora; something which we now find more easily accomplished with definitive antibiotics for coliform suppression. Lyon was equally insistent that "grave" anemias often cleared up following institution of his biliary drainage scheme and he specifically states that this procedure removed protein split products from a vantage point for entrance to the general circulation.[21] Groves,[22] basing his assumption on the constant indicanuria evinced by some anemic patients and that this indicated excessive intestinal putrefaction and absorption of products arising therefrom, claimed to have cured addisonian anemia by a sauerkraut diet. It is curious that this is a lactobacillus fermentation product. Almost half a century ago, Herter[23] suggested a relationship between hemolytic products formed by a normal stool inhabitant, B. aerogenes capsulatus (a proteolytic organism when the diet is proteinaceous) and addisonian anemia and Cornell[24] subsequently furnished clinical evidence for this thesis. Wells[11] has reviewed this entire subject just before the advent of liver therapy for addisonian anemia; the position of the review in the evolution of our knowledge makes it doubly worth perusing.

Greig and Holland[25] have recently shown that those drugs vitiating cholinesterase are capable of markedly increasing cellular permeability, even that of the erythrocyte from which the hemoglobin diffuses out. Should this sequence be assumed to occur in the bone marrow (which, in the human is the chief source of blood cholinesterase) the findings bid fair to clear up the controversies on the "hemolytic" nature of the estrapenic anemias as well as to establish the link that must exist between adrenocortical activity (which also regulates cellular permeability) and the bone marrow. Our present working hypothesis is that increased peptone, whether arising from the intestinal tract or otherwise, is capable of de-

pressing the hemopoietic marrow by vitiation of cholinesterase activity. B_{12} or folic acid may curtail this effect, in some instances, by augmenting cholinesterase production, though it must be borne in mind that both B_{12} and folic acid are "lactobacillus growth factors" and may accomplish the same end result in the intestinal tract as selective streptomyces antibiotics. Adrenocorticotherapy may operate in other instances, by decreasing the augmented permeability of the gut for peptones, by changing the route of protein catabolism so that less peptone is formed, or by a combination of these modalities. While there is evidence for all of these suggestions, they are still in the realm of theory. The fact remains that by the administration of relatively small amounts of antibiotic materials, previously refractory anemias seem now to be successfully treated.

Summary and Conclusions

Case reports of five patients with refractory anemia of the arbitrarily designated "hemolytic" type showed a hemopoietic response to the oral administration of various materials derived from antibiotic-producing streptomyces strains. The amount of antibiotic administered was so small that antibacterial action, except in the intestinal tract, seemed unlikely. Administration was accompanied by a change in intestinal bacterial flora from a proteolytic to a saccharolytic type. In some instances, effects comparable to those obtained by the administration of corticotropins or corticosteroids, were noted. It is suggested that proteoses ("peptones") arising from an intestinal tract containing a proteolytic flora may induce atopic reactivity of the hemopoietic marrow and the designation "hemolytic" as applied to this category of anemias is therefore called into question. Regardless of the future validation of the theoretic premises, it has been demonstrated that the antibiotics derived from streptomyces species may have a pronounced "hematinic" effect.

Addendum

Since submission of this report certain additional comments appear to be presently justifiable on the basis of further elucidation of the mechanism of observed effects. There appear to be more than nuances of difference between the results of administration of crude s. griseus residues and of the pure antibiotics derived from streptomyces species fermentation; no general superiority of the one over the other can be claimed in this connection, though the administration of one of these materials may operate successfully where the other has apparently failed in an individual case. In a significant percentage of hematologic patients, best results are obtained by optimal combinations of both types of material but again this optimum must be ascertained in each individual patient. However administered and in whatever combinations of antibiotic plus B_{12}, the unalterable fact emerges that *it is only when an odorless stool is instigated and maintained, continuously and relentlessly* that those with hematologic dyscrasias remain in some degree of remission. This simple indicator of the

abeyance of proteolysis within the bowel is an easy one to follow but by no means simple to induce in all patients; because of the rapid emergence of antibiotic resistant proteolytic strains, it may be impossible in other patients. The latter make up a considerable bulk of the failure series. Recently, experience with the coincident ingestion of L. acidophilus milk (rather than the unfermented milk upon which prior reliance was placed to maintain a predominantly saccharolytic flora) has been adopted as a routine measure in all patients with the more serious dyscrasias.

Our original schedule[6] consisted in the conjoint administration of large quantities of Tween 80-emulsified linseed oil in milk with s. griseus residue; this was routine in acute leukemic patients and it may now be instructive to state the reasons behind this complexity of "nutrients". By facilitating oil absorption with Tween 80 it was hoped to induce a mild ketosis with possible adrenocorticotropin elution (a suggestion of Dr. Jacob Halpern of Kings County Hospital) at the same time as the ordinarily low blood cholesterol level was raised (as ingestion of any vegetable oil will do). However there was also in mind the desire to use an induced lipemia to neutralize the effects of proteases;[26] we knew some proteolytic product to be involved in the myelosuppressive dyscrasias but had hardly, at the time, suspected the intestinal tract. Actually other, unsuspected mechanisms were set up by the oil-Tween-antibiotic-B_{12}-milk schedule. One was the definite, extra-hepatoportal, systemic absorption of B_{12} by its solution in fatty acid and direct carriage into the lacteals. The striking rubrescense seen in acute leukemic patients on this schedule[6] was undoubtedly on the basis of the definite androgenic effect (an exactly similar rubrescence is seen in patients on massive testosterone therapy) and the androgens have been widely employed in the malignant hematologic dyscrasias. Furthermore, it is a distinct impression that less difficulty arose from salt and water retention during crude s. griseus therapy than with pure antibiotic therapy. This difficulty is now being encountered, incidentally, with the mycobacteriostatic streptomyces antibiotics used protractedly in the treatment of tuberculosis.[27] Electrolyte imbalance, a definite adrenocorticomimetic effect of the streptomyces-derived antibiotics, constitutes a real hazard in the therapy outlined in the body of this report and many ultimate failures were due to its non-recognition before cardiac damage had ensued. It is legitimate to speculate as to whether a problematic diuretic action of systemically administered B_{12} [28] might not have circumvented this particular adrenocorticomimetic effect.[29]

For effects of this regime on non-hematologic conditions, tabulated in detail elsewhere[5] a more complete explanation appears in order. The corticotherapeutic effects are found restrictively in sick individuals in that category of atopic reactivity, who would presumably respond to ACTH or cortisone. Such sick individuals presumably do not respond to their illness by an adrenocorticotropin-corticosteroid "alarm" reaction; if they did they would not be in this particular morbidity bracket. Obviously, either their adaptative chain for the "alarm" reaction is disrupted or else there

is a "block" therein. The latter alternative seems to be the case; certain sick people do not respond by a complete eosinophilopenia to what, in a normal individual, would be an adequate stimulus.[30] Current studies by the writer's group indicates that terramycin, or any of the related antibiotics, when administered in such manner and dosage as to vitiate proteolysis within the gut and thereby curtail proteosemia, thereby removes one of the blocking agents to the autothonous liberation of ACTH. The alarm reaction mechanism, having been "poised" by the patient's condition, may now proceed to elicit the same therapeutic response as though ACTH or cortisone had been given substitutively.

SUMMARY OF THERAPEUTIC RESPONSES
IN ANEMIC COMPONENT OF CERTAIN HEMATOLOGIC DYSCRASIAS

Condition	*Cases Treated*	*Therapeutic Response*		
		Definite	*Equivocal*	*Negative*
Leukemia	(64)	(32)	(17)	(15)*
Acute	44	23††	11	10
Subacute	3	3	0	0
Chronic	(17)	(6)	(6)	(5)*
Myeloid	11	6	1	4
Lymphoid	5	0	5	0
Monocytic	1	0	0	1
Hodgkin's Lymphoma	7	4	1	2
Plasmocytic Myeloma	4	1	2	1
Purpura	(12)	(9)	(1)	(2)*
Thrombopenic	5	4	1	0
Allergic	4	3	0	1
Myelophthisic	3	2	0	1
Aplastic Anemia	4	1	2	1
Megaloblastic Anemia	8	7	1	0
"Hemolytic" Anemia	18	15	2	1
Periarteritis Nodosum	2	1	1	0
Erythremia†	4	0	4	0
Radiation Myelopathy**	15	11	2	2

*Numbers in parenthesis are totals of those in subordinate columns.
†Attempt at securing of reduction in erythrocyte count without adjuvant treatment.
**From therapeutic radiation for coexisting malignant condition.
††Includes nine known patients who survived for over one year.

Materials used in clinical studies were generously supplied by Chas. Pfizer and Co., Brooklyn, N. Y.

It is difficult at this time to completely evaluate the repercussions of this theory of antibiotic action on the therapeutics of the future though it is more than likely that a good percentage of the results ascribed to killing off bacteria, viruses, etc., were actually due to this covert effect on the humoral adaptative mechanism. The latter would naturally not work in cases of absolute functional or anatomic hypophyseal or adrenocortical inadequacy and consequently there have been no reported successes with terramycin, aureomycin or chloramphenicol in Simmon's or Addison's diseases. However the conditions extant in the latter are evidently not operative in the malignant hematologic dyscrasias as may be indicated by

the summary of results in the latter in Table I, which though hardly classifiable as a therapeutic panegyric, does represent concrete progress even if it may turn out to be rejuvenation of an extremely old modality.

It is of interest that during the progress of presently incorporated studies, Gannslen announced comparable sustentive and therapeutic effects in leukemia and Hodgkin's disease, which he now regards as curable, by continuous protracted sulfathiazole administration. Sulfathiazole has comparable "animal protein factor" effects in domestic animals that respond by augmented growth to terramycin, aureomycin or chloramphenicol ingestion; like the latter, the sulfonamides are coliform suppressors. With this last piece of evidence, the present status of minimal oral antibiotic therapy may be summed up with the statement that its effect in general is through modification of the intestinal bacterial flora.

REFERENCES

1. Cunha, T. J., Hopper, H. H., Burnside, J. E., Pearson, A. M., Glasscock, R. S., and Shealy, A. L., *Arch. Biochem.* 23:510, 1949.
2. Barnard, R. D., and Appel, A., *Urol. and Cutan. Rev.* 54:345, 1950.
3. Wetzel, N. C., Fargo, W. C., Smith, J. H., and Helikson, J., *Science* 110:651, 1949.
4. Report to Clinical Pathology Conference, Kings County Hospital, Brooklyn, N. Y., 14 June, 1949.
5. Barnard, R. D., In Press.
6. Barnard, R. D., and Fox, H. F., *Ohio State M. J.* 46:748, 1950.
7. Waksman, S., *Streptomycin*, 1949, p. 240.
8. Mitchell, H. K., Snell, E. E., and Williams, R. J., *J. Am. Chem. Soc.* 63:2284, 1941.
9. Barnard, R. D., Gordon, G. B., and Weitzner, H. A., *Am. J. Dig. Dis.* 16:401, 1949.
10. Barnard, R. D., *J. Lab. & Clin. Med.* 28:1568, 1943.
11. Wells, H. G., *Chemical Pathology*, Saunders, 1925.
12. Emerson, C. R., *Blood* 3:515, 1948.
13. Barnard, R. D., *N. Y. State J. Med.* 50:1852, 1950.
14. Isaacs, R. J., *Blood* 3:335, 1948.
15. Davis, J. E., *Science* 104:605, 1946.
16. Barnard, R. D., and Mentha, J. W., *Science* 107:195, 1948.
17. Barnard, R. D., *N. Y. State J. Med.* 47:2703, 1947.
18. Vaughn, V. C., *Protein Split Products*, Philadelphia, 1913.
19. Metchnikoff, L., *Ann. Inst. Pasteur* 27:873, 1914.
20. Barnard, R. D., *Ohio State M. J.* 44:801, 1948.
21. Lyon, B. B. V., *Non-surgical Drainage of the Gall Tract*, Philadelphia, 1923.
22. Groves, A. A., *Trans. Royal Alexandra Hospital*, Ontario, 1916.
23. Herter, C., *J. Biol. Chem.* 2:1, 1906.
24. Cornell, B. S., *Canad. Med. Assn. J.* 15:26, 1925.
25. Grieg, M. E., and Holland, W. C., *Fed. Proc.* 8:297, 1949.
26. Jobling and Petersen, cited by 11.
27. Werner, C. A., Tompsett, K., Muschenheim, C., McDermott, W., *Am. Rev. Tuber.*, 63:49, 1951.
28. Barnard, R. D., and Weitzner, *Lancet*, 2 717, 1949.
29. Barnard, R. D., *N. Y. State J. Med.*, 51:534, 1951.
30. Brenner, L. O., Waife, S. O., and Wohl, M. G., *J. Lab. & Clin. Med.*, 37:593, 1951.
31. Gannslen, E., *Folia Hematologica*, 70:1, 1950.

Chronic Infection and the Non-Specific Reaction

HOWARD B. EMERSON, JR., M.D.*

From the use of certain agents in specific conditions further evidence may be adduced in support of the relation between focal infection and systemic disease.

Undecylenic acid was recently used by Perlman[1] in the treatment of psoriasis, neurodermatitis and arthritis. The occurrence of headache and folliculitis noted by some of his patients during treatment, i.e., evidence of a focal reaction in commonly infected sites suggested to me that the drug exerted its effect by inducing the non-specific reaction. Upon clinical trial this was found to be the case. In determining the dose patients were advised to take four capsules (0.44 gm. each) at bed-time, increasing by one capsule nightly. It was found that a focal reaction in the upper respiratory tract, as evidenced by increased post-nasal discharge, relief of nasal obstruction, headache, etc., occurred in a few individuals after taking four capsules. In most a reaction was noted at six or seven capsules with the "peak" reaction occurring at about nine capsules (i.e. the reaction following which local and general symptoms improved markedly and reactions diminished in severity even though the dose was raised). Only the "peak" reaction was shocking (Perlman's nitritoid reaction?). In hyporeactors 20 capsules did not produce a focal reaction nor was there any shock reaction. (The non-specific reaction can be easily recognized clinically and consists of fatigue, malaise, hyperirritability, fever, tachycardia and diuresis. Frequent sequelae are drowsiness and weakness. A focal reaction occurs in any infected site. In the upper respiratory tract it is evidenced by an increase of the nasal discharge (usually post-nasal), congestion or decongestion of the nose, headache, sore throat, etc.) At first a nightly dose of 10 capsules of undecylenic acid was continued until presumptive cure was obtained. However, in patients previously treated by a series of foreign protein injections subcutaneously[2] given twice weekly it was found that the time required to obtain a presumptive cure with undecylenic acid given daily was about the same. Therefore, patients were advised to take the capsules only twice weekly (see "stage of resistance" below). A dose of 4.4 gm. of undecylenic acid was felt to be in excess of that required by most individuals to elicit the maximum response. In patients in whom "heartburn" was a manifestation of chronic infection the drug was poorly tolerated and subcutaneous foreign protein therapy was given instead. Otherwise, for a time, I used undecylenic acid therapy in the treatment of chronic infection of the upper respiratory tract and its protean systemic manifestations and in allergic states whether due to bacterial or pollen sensitivity. Because of the size of the undecylenic acid capsule I did not use the drug in young children.

Glutamic acid was recently reported by Waelsch[3] to be of value in epilepsy. An increase in intelligence in children given this amino acid was reported by Zimmerman[4]. Since my own experience in the treatment of epilepsy using subcutaneous foreign protein therapy confirmed that of

*Active Medical Staff, Allegheny Valley Hospital, Tarentum, Pennsylvania.

others in the past that "idiopathic" epilepsy was a reaction to chronic infection I felt that glutamic acid might exert its effect by inducing the non-specific reaction. Upon clinical trial this proved to be the case. Four grams of the acid (in a single dose) were found to produce the usual focal and systemic effects of the non-specific reaction in both children and adults. Increasing the dose to eight grams did not increase the reaction. The systemic reaction was always mild. The "peak" reaction was not elicited. Patients with or without epilepsy in whom the chronic infection had first been brought under control by means of subcutaneous foreign protein therapy felt no brighter mentally while taking glutamic acid. As with undecylenic acid, patients reacting poorly to foreign protein injections also reacted poorly to glutamic acid and conversely. Since it appeared that glutamic acid was not a substance capable of eliciting the maximum response (and therefore not capable of bringing about cure of chronic infection), I discarded it as being of only palliative value. Over 8 gm. of sodium glutamate at a single dose taken by a good reactor (the author) did not elicit any signs or symptoms of the non-specific reaction.

From a review of the recent monography of Kalinowsky and Hoch[5] on "Shock Treatments in Psychiatry," it is evident that the phenomena such as leukopenia followed by leukocytosis, fever and the "aggravation" of foci observed during non-specific therapy have been noted following the use of the various shock treatments. That the shock treatments used in psychiatry are not specific for mental disease has been demonstrated by Godlowski[6] who treated asthma successfully with insulin shock. Interesting also is the report from Italy of the use of electro-shock therapy in the treatment of peptic ulcer.[7] Evidence for the adrenocortical response following electro-shock therapy has been presented by Altschule.[8] There can be little doubt that the various shock treatments used in psychiatry exert their effect by inducing the non-specific reaction.

It has long been known that roentgen rays also will induce the non-specific reaction. Kelly and Dowell[9] have used roentgen ray treatment in many acute infections. It is worthy of note in this connection that Hedfield[10] has used roentgen therapy in over 800 patients with peptic ulcer with good result.

Understanding of the common denominator of these agents discussed above is simplified if it be appreciated that non-specific therapy is a controlled means of inducing the "alarm" reaction which is modified by the presence of infection. Selye[11] states that the "alarm" reaction consists of a "shock phase" characterized by tachycardia, decrease in muscular tone and body temperature, formation of transient gastric and intestinal ulcers, anuria, oedema, hemoconcentration, decrease in blood chlorides, acidosis, transitory rise, followed by a decrease in blood sugar, leukopenia followed by leukocytosis and discharge of adrenalin from the adrenal medulla. This phase may last for a few minutes to 24 hours. Overlapping this phase somewhat is the "counter-shock" phase characterized by enlargement of the adrenal cortex, acute involution of thymus and lymphoid organs and reversal of most signs of the shock phase, i.e., blood dilution and increase

in blood volume, increase in blood chlorides and blood sugar, alkalosis, diuresis and often a rise in body temperature. The blood coagubility is increased. This phase is followed by a stage of resistance to the eliciting stimulus.

Selye lists many of the insults to the body which elicit the "alarm" reaction: arterial occlusion, traumatic and obstetric shock, hemorrhage, burns, bacterial toxins, anesthesia, certain drugs, oestrogens, etc. I would like to emphasize that following any of these insults a focal reaction in the upper respiratory tract will also be noted when infection is present. The occurrence of black stools or epigastric pain or "heartburn" following an occasional injection of foreign protein suggests that gastro-intestinal ulcers do occur during treatment of chronic infection. Their probable occurrence, however, I do not feel to be a contraindication to the treatment of peptic ulcer with non-specific therapy, particularly since 200 mg. of enterogastrone[12] taken intramuscularly by the author elicited the characteristic signs and symptoms of the "alarm" reaction. Similarly one tablespoonful of "Viodenum"*, a raw duodenal substance used with benefit in peptic ulcer and ulcerative colitis, taken by the author also induced the "alarm" reaction. Selye noted that ulcers could be prevented by the administration of glucose, without otherwise altering the "alarm" reaction. Again, I do not feel that the increased coagubility of the blood contraindicates the use of non-specific therapy in thrombophlebitis since my own experience has shown that patients with this disease who can be kept free of chronic infection are free of phlebitis. Furthermore, the use of foreign protein therapy (intravenous typhoid vaccine) has been found to be effective treatment of thrombophlebitis in the past.[13]

Selye also pointed out that in the absence of the adrenal cortex the countershock reaction is negligible or absent. That the administration of one adrenocortical substance (Compound E) is not an effective substitute for the "alarm" reaction, however, has recently been shown by Hench[14] and his associates. By giving large doses daily of this substance to patients with arthritis, arthritic symptoms were, for the most part, suppressed but recurred on cessation of treatment. Whether chronic administration of Compound E may not produce a functional hypoadrenalism (Selye) and decrease the individual's resistance to shocks following withdrawal of the hormone remains to be seen. Evidence that the administration of adrenocorticotropic hormone (also used by Hench) does not produce the same changes in the urea-creatinine ratio as the "alarm" reaction (electroshock therapy) has also been presented by Altschule.[8]

The use of undecylenic acid in the treatment of chronic infection demonstrates that the shock need not be severe to elicit the maximum counter-shock reaction. In giving subcutaneous foreign protein injections the shock produced is occasionally unnecessarily severe. In using any controlled means of producing the "alarm" reaction in patients with chronic infection it is evident that the reaction is a function of the "depth" of infection as well as of the dose of the eliciting agent (until the dose eliciting the maximum response is reached) but is also basically governed

*Viobin Corp., Monticello, Illinois.

by the patient's ability to react and further experience in the treatment of patients with chronic infection has strongly indicated that the reactibility is hereditary. Raising the dose to any amount does not change the basic reactibility of the individual but because of variation in reactibility over a period of time a "peak" reaction may not be noted in some patients until a relatively large dose of foreign protein is given. In using foreign protein therapy the dose must be raised because of tolerance but the same phenomenon of delayed response occurred in using undecylenic acid when the dose was constant at 4.4 gm. Further experience with non-specific therapy has confirmed the fact that the patient's response is diminished during warm weather. In my original publication[2] I mentioned, in addition to the "hyporeactor" the patient "whose reactions, although good, always fell short of cure." The number of these patients increased during the summer and many patients in whom a presumptive cure was obtained in a reasonable time during cold weather fell into this group during warm weather. Further observation of patients receiving non-specific therapy has also demonstrated that in the female, reactions were better at the menstrual period and during pregnancy. In treating one patient in the latter half of pregnancy (7 months) a presumptive cure of her chronic infection of the upper respiratory tract was obtained in 7 injections of foreign protein subcutaneously during the summer. Retreatment for a reinfection following a "cold" post-partum during the (admittedly mild) winter necessitated 16 injections to obtain a presumptive cure. One other patient required 26 injections before pregnancy. Following a recurrence, retreatment was begun when she was 2 months pregnant. Reactions were much more severe and a presumptive cure was obtained after 9 injections. Because of the above observations progesterone (in 25, 50 and 100 mg. doses intramuscularly) was given to a number of poor reactors twice weekly for from 1 to 4 injections but without any appreciable effect on the reactions from foreign protein. Progesterone, although an ovarian hormone, is also secreted by the adrenal cortex of both male and female and has been found to be an effective substitute for adrenal cortical extract in keeping adrenalectomized ferrets[15] alive. More vigorous use of progesterone[16] might have produced an appreciable change in some systemic diseases but because of side effects on the menstrual period, its possible effect upon the prostate gland of elderly males and because of another possible disadvantage mentioned in connection with Compound E its use was not pursued.[17]

The hyporeactor occurs in all age groups although in the relatively small number of children seen by me in a practice limited to internal medicine a presumptive cure of infection has always been obtained with persistent treatment. The reactive state of the hyporeactor could not be correlated with menstrual disturbances, body build or any predisposition to develop a particular type of systemic disease. Their systemic and local symptoms of infection were no worse than those of the good reactors. Their susceptibility to "colds" and other acute illness was no greater than that of good reactors. There was never any clinical evidence in members of the hyporeactor group of hypoadrenalism or hypopituitarism. The

hyporeactor therefore must react well to living parasites whether by the same mechanism as that of the good reactor or by some other mechanism.

In continuing a search for substances which may act as adjuvants to or substitutes for, non-specific therapy of the "alarm" reaction type I became interested in the following drug:

Ortho-Iodoxybenzoic acid was first used by Young and Youmans[18] in 1927 in the treatment of arthritis. Young and Youmans recognized that this drug was an agent inducing a non-specific reaction but that the reaction was not the same as that produced by foreign protein since individuals who did not respond to foreign protein did respond to ortho-iodoxybenzoic acid. My own experience confirmed this observation. Ortho-iodoxybenzoic acid has been shown to produce leukocytosis[19] (not preceded by leukopenia), a rise in antibodies,[20] and occasionally fever. It did not prevent systemic allergic reactions but diminished local allergic inflammation to an antigen to which the organism was sensitive. The drug did not produce iodism.[21] It produced indicanura in 96% of patients with arthritis. Administration of the drug caused an increase in capillary permeability and an increase in lymph flow of 400%.[22] It is interesting that administration of the drug caused a gradual fall in blood pressure and an improvement in heart conditions in many patients (Wheeldon). The drug was originally used intravenously but the calcium salt (oxoate-B*) was used by Wheeldon orally. The dose was 0.5 gm. q.i.d. There were no unpleasant side reactions with this type of treatment as were reported from its intravenous use. (Chiefly nausea and vomiting associated with a feeling of apprehension.)

To the above observations I would like to add my own that "Oxoate-B" produces a focal reaction in the upper respiratory tract as indicated by headache and an increase of the post-nasal discharge. The post-nasal drip gradually diminishes and disappears if the patient reacts consistently. However, I found progress to be slow and uncertain on any dosage schedule or interval. I used the drug only during the summer months. In giving more than 0.5 gm. of the drug at a single dose reactions (nausea and vomiting) were unpredictable and were severe enough in some cases that I have not felt that this particular drug was feasible for general use on ambulatory patients except by the method advised by Wheeldon. The reaction produced by the salts of ortho-iodoxy benzoic acid can be differentiated clinically from the "alarm" reaction by the following characteristics:

Drowsiness occurs during rather than after the reaction. Fatigue, malaise and diuresis are slight. Forceful beating of the heart and tachycardia are not usually noted. The nausea is not a true nausea but (if the dose is not great enough to produce frank vomiting and retching) consists of a feeling of heaviness in the epigastrium which may sometimes amount to a "knot" and a feeling that vomiting is about to occur. This feeling occurs within a few hours of oral administration of the drug and is transient. However, frequently associated is substernal pain, apprehension, and heartburn only partially relieved by antacids. The reaction strongly sug-

*Smith, Kline and French, Philadelphia, Pennsylvania.

gests an autonomic nervous system overplay. If so the state of the autonomic nervous system might explain the variable occurrence of the annoying portion of the reaction from ortho-iodoxy benzoic acid using the same dose in the same individual. The focal reaction in the upper respiratory tract differed from that produced by agents inducing the "alarm" reaction in that the increase in nasal discharge was less marked and the mucous more tenacious.

Certain adjuvants used in treating patients with "alarm" reaction therapy were not previously reported and I believe it worthwhile to discuss these below before presenting several other agents found to induce the "alarm" reaction.

Adjuvants to Non-specific Therapy

In the treatment of patients with chronic infection fatigue was a symptom complained of by the majority. These symptoms often improved rapidly under non-specific therapy but in some patients continued and often increased, particularly following a series of good reactions. This fatigue was replaced by a feeling of vigor and well-being upon the administration of para-amenobenzoic acid (0.2 gm. t.i.d.) for several days. The vitamin was continued until treatment was completed. The effect was sustained when the vitamin was withdrawn. Given early in the treatment 4 gm. of Paba daily did not produce any appreciable effect. Given in larger doses, however, to patients with acute rheumatic fever, Rosenblum and Fraser[23] noted a beneficial effect on the symptoms of the disease and a sense of well-being out of proportion to the temperature. The effect as used in connection with non-specific therapy is probably a vitaminic one. The necessity of using large doses in rheumatic fever suggests that the deficiency is made up with difficulty in the presence of untreated infection.

Adrenalin in oil (1:500)[24] given in 1 cc. doses, or three minims of the aqueous (1:1000) solution has served to give a "boost" to patients reacting poorly during non-specific therapy but its continued use did not appear to produce any spectacular advance toward cure and because of the usual annoying effects of palpitation, tremulousness, etc.—I discontinued its use. (If the release of adrenalin is a necessary part of the "alarm" reaction either the amount secreted is small or the kind of adrenalin is not the same as that given parenterally since the patient familiar with the "alarm" reaction will note only a slight transient tremulousness within a few minutes to a few hours after administration of an agent inducing the "alarm" reaction. Apparently the natural "alarm" reaction is a "mass" reaction and cannot be induced by substitution at the distal end, by adrenal cortical extracts, or at the proximal end, by adrenalin.)

Potassium acetate[25] (2 gm. t.i.d.) and calcium gluconate[26] (2 gm. t.i.d.) given orally singly or together in a number of patients during non-specific therapy did not appear to affect the patients' reactions.

Ascorbic acid[27] (2 gm. daily) given orally over a period of two weeks did not exert any appreciable effect on the reactions of a number of patients.

Thiamin chloride, given in doses of 50–100 mg. intramuscularly to patients with tenderness over the supraorbital and infraorbital nerves usually lessened the strong tendency toward headache in these individuals.

Repetition of the injection was often necessary until the infection was controlled.

Since "colds" are intimately linked with the problem of chronic upper respiratory infection the use of bismuth as an adjuvant to non-specific therapy, as I previously reported, should not be forgotten. The continued use of bismuth in combination with an agent inducing the non-specific reaction as treatment of a "cold" occurring during non-specific therapy has confirmed the value of the treatment. The use of bismuth in the treatment of another virus disease—verrucae—has been previously reported[28]. It will be recalled also that bismuth has been found to be effective in infectious mononucleosis although Saltzman[29] believed the result to be due to the action on secondary (bacterial) invaders. Monteiro[3] found bismuth therapy to be dramatically effective in streptococcal tonsillitis. Pneumococcal and staphylococcal infections did not usually respond. Bismuth is known to produce a non-specific reaction with leukocytosis, etc. However, it does not produce the "alarm" reaction. On the contrary, clinically the reaction from the administration of bismuth has all the characteristics of the reaction produced by the salts of ortho-iodoxy benzoic acid when given in small doses (0.5 gm.). However, bismuth also has its own well known side reactions.

Aureomycin proved to be a valuable drug during a recent epidemic of severe upper respiratory infections. Patients with this infection did not present the clinical characteristics of the common "cold." They did not respond to combined bismuth and non-specific therapy, to penicillin, nor to sulfadiazine.

I have not used antihistaminics for "colds" or for allergic conditions because of the report of Halpern[31] that antihistaminics interfere with localization of infection, although it is possible that the antihistaminics may exert a pharmacologic action similar to that of bismuth in addition to their antihistaminic effect.

Other Agents Inducing the Non-specific Reaction

In a search for a substance which could be given by mouth to both children and adults in the treatment of chronic infection, inositol was found to be very satisfactory. It is marketed in 500 mg. capsules and this amount was found to be capable of eliciting the maximum response of the "alarm" reaction type. By dividing one capsule into 100 mg. capsules and administering the vitamin to myself in increasing doses I determined that the "peak" reaction was produced at a dose of 400 mg. I have used the same dose (500 mg.) in child or adult since one need not fear an overdose, the reaction from this substance being limited by the maximum response of the host. Patients were advised to take the drug twice weekly on an empty stomach.

Inositol was used in combination with vitamin E by Milhorat and Bartels[32] in patients with progressive muscular dystrophy and was found to diminish creatinuria in this disease as well as in Grave's disease. It was necessary to give the drugs orally and therefore the action was believed to be due to a condensation product of inositol and a-tocopherol. An in vitro condensation product was found to be more effective than giving the two

drugs separately by mouth in patients with muscular dystrophy.

It will be recalled that vitamin E has been found to be an effective substitute for oestrogens in controlling menopausal symptoms,[43] and that there is a rise in oestrogens preceding the menstrual period. Vitamin E has the advantage over oestrogens in that it does not cause changes in the vaginal mucosa and may be safely given to patients with cancer. Furthermore, by trial on myself following a reinfection of the upper respiratory tract I determined that vitamin E was itself capable of eliciting the "alarm" reaction (1000 mg. taken at a single dose resulted in the characteristic symptoms of the "alarm" reaction; 500 mg. taken on a different occasion elicited a similar reaction). The systemic reaction was mild.

Hyporeactors did not react to inositol, nor to inositol given with 100 mg. of alpha-tocopherol. But by raising the amount of alpha-tocopherol. by 100 mg. at each successive administration of the vitamins it was found that patients who, although poor reactors, reacted occasionally, a focal and systemic reaction was produced when a dose of 300 mg. of alpha-tocopherol was reached. In several patients who had never shown evidence of reaction at all after prolonged treatment with undecylenic acid or foreign protein or with inositol and 100 mg. of alpha-tocopherol, a typical "alarm" reaction was produced when a dose of 400 mg. of alpha-tocopherol was reached. The reaction did not appear to be more severe when 500 mg. or more of alpha-tocopherol was given. On myself, a good reactor, after inducing the "peak" reaction with 500 mg. of inositol and taking several more doses beyond the "peak" I began adding alpha-tocopherol, beginning with 100 mg. and increasing with each dose by 100 mg. A secondary "peak" reaction occurred when 200 mg. of alpha-tocopherol were taken indicating that the good reactor's response could also be improved by alpha-tocopherol. None of the "hyporeactors" went on to presumptive cure within a period of three months although all received marked benefit, both local and systemic, when 500 mg. each of inositol and alpha-tocopherol were given twice weekly. This dose was used as a standard on all new patients when the above noted relationships became manifest.

During several years' experience in the treatment of chronic infection with non-specific therapy an occasional patient was found who reacted well initially but whose re actions faltered later in the treatment, with a regression of the state of health to the original level. A few others were seen who, when retreated following a recurrence of infection were slower to respond during the second series of treatments or fell into that group of patients who always fell short of presumptive cure. It was my impression also that acute infections of the upper respiratory tract in these patients were more severe than one would ordinarily expect. These phenomena suggested a developing deficiency probably induced by repeated reactions and probably also increased by warm weather. More attention, was therefore paid to diet, emphasizing a high protein ration in view of the well known work of Cannon on the affect of protein on resistance to infection. Although patients on a high starch, low protein diet felt better when the protein was increased this measure alone did not accelerate presumptive

cure. Nor was I impressed by the effect of polyvitamin capsules, including one which contained, in addition to the usual vitamins, the trace elements.

d-Biotin, however, was found to stimulate the reaction in most patients. Moreover, it was found to be itself capable of inducing the "alarm" reaction and in addition of eliciting the maximum response. Using a capsule containing 0.2 mg. of d-biotin the "peak" reaction in a child was produced by 0.2 mg., in adults by 0.6 or 0.8 mg. Hyporeactors did not react to d-biotin unless "primed" with alpha-tocopherol. In good reactors a secondary "peak" was reached when alpha-tocopherol was administered with d-biotin. The treatment was therefore again standardized by giving all adult patients 500 mg. of alpha-tocopherol and 1.0 mg. of d-biotin simultaneously twice weekly on an empty stomach. In children only d-biotin was given unless the patient was, from previous experience, known to be a poor reactor in which case 300 mg. of alpha-tocopherol were added. The administration of d-biotin appeared to do no more than to restore patients to their original or optimum level of reaction but it did not make good reactors out of hyporeactors.

Recently vitamin B_{12} became available in tablet form. Wetzel[34] and others reported the use of ten micrograms daily in eleven children with simple growth failure and malnutrition. Five responded dramatically with rapid increase in vigor, alertness and appetite and better behaviour. In one case symptoms of a severe allergic bronchitis vanished in one week. On the basis of this report one might reasonably expect that vitamin B_{12} would be found to exert an effect against chronic infection. Upon clinical trial, however, it did not induce the "alarm" reaction. On the contrary the reaction could not be differentiated clinically from that produced by ortho-iodoxy benzoic acid or bismuth (vide sopra). Following the administration of liver extract in patients with pernicious anemia certain effects such as leukocytosis, increased metabolism, fever, nasal discharge, substernal pain and vomiting have been noted[35] and are undoubtedly manifestations of the non-specific effect of vitamin B_{12}. The reaction was noted in adults taking 20 mcg. at a single dose. The treatment was therefore again standardized by incorporating 0.5 mg. of d-biotin and 10 mg. of vitamin B_{12} in a single capsule and giving one to a child, two to an adult twice weekly along with alpha-tocopherol as noted above. Patients were instructed to take the capsules daily in case of a "cold." It goes without saying that the use of bismuth was discontinued upon the addition of vitamin B_{12} to the treatment of chronic infection of the upper respiratory tract. Further experience will demonstrate the value of the combined treatment in chronic infection as well as in the treatment of "colds." I have not felt it worth while to reevaluate the results statistically at this time since the treatment is not yet static.

Comment

Appreciation of the common denominator of a wide variety of agents makes it possible to integrate many isolated observations, only a few of which can be mentioned here, and also to discard many impractical agents. Recently Sackler[36] used injections of histamine in the treatment of psychotic patients and felt that the results obtained were as good as those which

could be obtained with shock therapy. In view of the fact that histamine is known to induce the non-specific reaction, the results are not surprising.

d-Biotin has been found to favorably effect the paralysis in animals on a potassium deficient diet.[37] It is possible that this effect can be explained on the basis of the electrolyte shift occurring during the "alarm" reaction and does not necessarily mean that d-biotin has a specific effect on potassium metabolism. Similarly the poor resistance of d-biotin deficient chicks to malaria[38] may be explained on the basis of an inadequate non-specific response to the infection and does not necessarily indicate that d-biotin has any specific effect on resistance. It cannot be denied that the "non-specific" reaction is specific enough, however.

Inositol has been reported to inhibit the growth of cancer.[39] Realization of the fact that this vitamin will induce the "alarm" reaction places it along with other agents in the same class with Coley's serum[40] and the polysaccharide of Shear.[41] It is possible that infection, whether acting locally or remotely may in vivo create deficiencies which lead to malignant change. If this hypothesis is to be tested it is obvious that all infections must be eradicated in the cancer (but particularly the pre-cancer) patient and all deficiencies made up.

The application of a treatment for chronic infection as developed above to certain specific infections should not be lost. Recently Kropp and Floyd[42] injected a lipopolysaccharide extracted from virulent tubercle bacilli into patients with advanced tuberculosis. The results were excellent. Close attention to the report of these authors reveals that many of the "unexplained" reactions in the experimental animal (e.g. fever following an injection of the extract in tuberculin-negative animals) and in human patients (e.g. the delay in the appearance of systemic reactions during the course of treatment) could (as well as the results of treatment) easily be interpreted in terms of "alarm" reaction therapy.

When it becomes evident that certain naturally occurring substances will control or cure chronic bacterial infection one wonders whether such factors may not be operative in a race as healthy as the Hunzas.[43] However, until such time as the secret is learned it will probably be necessary to supply the necessary factors in capsule form.

Summary

1. The identity of the non-specific reaction and the "alarm" reaction is noted.
2. A number of agents found to induce the "alarm" reaction are discussed.
3. A number of agents which induce a non-specific reaction different from the "alarm" reaction are also discussed.
4. The application of the use of agents of both types in the treatment of chronic infection is described.

References

1. (a) Perlman, H. H.: "Undecylenic Acid in Psoriasis and Neurodermatitis," *J. A. M. A.* 139:444, 1949. (b) Perlman, H. H.: "Undecylenic Acid by Mouth in the Treatment of Arthritis and Bursitis," *Urol. & Cutan. Rev.* 53:103, 1949.
2. Emerson, H. B., Jr.: "The Biologic Cure of Chronic Infection," *M. Rec.* 162:6, 1949.
3. Waelsch, Heinrich and Price, J. C.: "Biochemical Aspects of Glutamic Acid Therapy for Epilepsy," *Arch. Neurol. and Psychiat.* 51:393, 1944.
4. Zimmerman, F. T., Burgermeister, B. B. and Putnam, T. J.: "The Ceiling Effect of Glutamic Acid Upon Intelligence in Children and Adolescents," *Am. J. Psychiat.* 104:593, 1948.

5. Kalinowsky, L. B. and Hoch, P. H.: *Shock Treatments and Other Somatic Procedures in Psychiatry*, Grune and Stratton, New York, 1949.
6. Godlowski, Z.: "Insulin Shock Treatment of Bronchial Asthma," *Brit. Med. J.* 1:717, 1946.
7. Corbella and Piredda: "Peptic Ulcer and Electroshock," *J. A. M. A., Foreign Letters* 140:424, 1949.
8. Altschule, M. D., Altschule, L. H. and Tillotson, K. J.: "Changes in Urinary Uric Acid—Creatinine Ratio After Electrically Induced Convulsions in Man," *J. Clin. Endocrinol.* 9:548, 1949.
9. Kelly, J. F. and Dowell, D. A.: *Roentgen Treatment of Infections*, The Year Book Publishers, Inc., Chicago, 1942.
10. Hedfield, A.: "Roentgen Therapy in Gastric Ulcer," *Strahlentherapie*, Berlin 77:387, 1948. Abstracted in *J. A. M. A.* 140:846, 1949.
11. Selye, Hans: "The General Adaptation Syndrome and the Diseases of Adaptation," *J. Clin. Endocrinol.* 6:117, 1946.
12. Ivy, A. C.: "The Prevention of Recurrence of Peptic Ulcer, An Experimental Study," *Gastroenterology* 3:443, 1944.
13. Tice, Frederick: *Practice of Medicine*, Vol. 6:51, W. T. Prior Co., Hagerstown, Md., 1940.
14. Hench, P. S., Kendall, E. C., Slocumb, C. N. and Polley, H. F.: "The Effect of a Hormone of the Adrenal Cortex (17 Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocortidotropic Hormone on Rheumatoid Arthritis," *Proc. Staff Meet. Mayo Clin.* 24:181, 1949.
15. Gaunt, Robt. and Hays, H. W.: "Role of Progesterone and Other Hormones in Survival of Pseudopregnant Adrenalectomized Ferrets," *Am. J. Physiol.* 124:767, 1938.
16. Reich, N. E.: "The Use of Large Doses of Progesterone in Rheumatoid Arthritis," *Am. Pract.* 4:1, 1949.
17. Clausen, H. J.: "The Atrophy of the Adrenal Cortex Following the Administration of Large Amounts of Progesterone," *Endocrinol.* 27:989, 1940.
18. Young, A. S. and Youmans, J. B.: "The Use of O-Iodoxybenzoic Acid in the Treatment of Infectious Arthritis," *J. A. M. A.* 87:746, 1926.
19. Loewenhart, A. S. and Grove, W. E.: "Studies on the Pharmacological Action of Oxidizing Substances," *Jour. Pharmacol. and Exper. Therap.* 3:145, 1911.
20. Hektoen, Ludwig: "The Influence of Sodium Iodoxybenzoate on the Production of Antibodies in Dogs," *Trans. Chicago Path. Soc.* 8:138, 1909–11.
21. Cottrell, J. E.: "The Treatment of Arthritis with Salts of O-Iodoxybenzoic Acid," *Am. J. Med. Sci.* 174:623, 1927.
22. Wheeldon, Thomas: "The Use of Calcium Ortho-Iodoxybenzoate in the Treatment of Arthritis with a Discussion of Its Possible Value in Some Other Orthopedic Conditions," *Ann. of Int. Med.* 7:1540, 1934.
23. Rosenblum, Herman and Fraser, L. E.: "Effect of PABA on Fever and Joint Pains of Acute Rheumatic Fever," *Proc. of the Soc. Exper. Biol. & Med.* 65:178, 1947.
24. Soffer, L. J.: *Diseases of the Adrenals*, Lea and Febiger, Philadelphia, p. 46, 1948.
25. Lagoa, F. R.: "Potassium and Bacterial Infections," *J. A. M. A. Foreign Letters* 137:1332, 1948.
26. Hicks, C. L.: "Non-specific Therapy and the Vegetative Regulation of the Body," *M. J.*, Australia 2:171, 1936.
27. Dugal, Louis—Paul & Therien, Mercedes: "The Influence of Ascorbic Acid on the Adrenal Weight During Exposure to Cold," *Endocrinol.* 44:420, 1949.
28. O'Connor, W. B. and Tweedall, D. C.: "Bismuth Therapy of Verrucae," *J. Missouri M. A.*, pp. 25–26, Jan., 1948.
29. Saltzman, M.: "The Therapeutic Effects of Bismuth in Infectious Mononucleosis: A Preliminary Statement with Report of Two Cases," *Laryngoscope* 52:697, 1942.
30. Monteiro, A.: "Bismuth in Tonsillitis," *Arch. Otolaryng.* 34:719, 1941.
31. Halpern, B. N.: "Antihistaminics," *J. A. M. A. Foreign Letters* 139:802, 1949.
32. Milhorat, A. T. and Bartels, W. E.: "The Defect in Utilization of Tocopherol in Progressive Muscular Dystrophy," *Science* 101:93, 1945.
33. Christy, C. J.: "Vitamin E in Menopause," *Am. J. Obst. & Gynec.* 50:84, 1945.
34. Wetzel, N. C., Fargo, W. C., Smith, Lula H. and Helikson, Josephine: "Growth Failure in School Children as Associated with Vitamin B_{12} Deficiency-Response to Oral Therapy," *Science* 110:651, Dec., 1949.
35. Wintrobe, M. M.: *Clinical Hematology*, Lea and Febiger, Philadelphia, 1947, pp. 333–336.
36. Sackler, A. M., Sackler, M. D. and Sackler, R. R.: "Non-Convulsive Bio-Chemotherapy with Histamine," *J. Nerv. and Ment. Dis.* 110:149, 1949.
37. Smith, S. G.: "Potassium vs. Biotin in the Treatment of Progressive Paralysis in Dogs," *Proc. Soc. Exper. Biol. and Med.* 63:339, 1946.
38. Trager, W.: "The Influence of Biotin upon Susceptibility to Malaria," *Science* 97:206, 1943.
39. Herbst, W. P. and Bagley, C. E.: "Observations in the Use of Inositol in Advanced Malignancy of the Genito-Urinary Tract," *J. Urol.* 59:595, 1948.
40. Loeb, Leo: "The Treatment of Inoperable Sarcoma by Erysipelas and Prodigious Toxins, *J. A. M. A.* 54:262, 1910.
41. Creech, H. J., Hankwitz, R. F. and Wharton, D. R. A.: "Further Studies of the Immunological Properties of Polysaccharides from Serratis Macresans (Bacillus Prodigiosus). I. The Effects of Passive and Active Immunization on the Lethal Activity of the Polysaccharides," *Cancer Research* 9:150, 1949.
42. Kropp, G. V. and Floyd, C.: "Use of Lipo-Polysaccharide Fraction in Treatment of Tuberculosis," *Yale J. Biol. & Med.* 20:27, 1947.
43. Rodale, I. S.: *The Healthy Hunzas*, Rodale Press, Emmaus, Pa., 1949.

Carcinogenesis

In the Light of the Trophoblastic or Unitarian Thesis of Cancer

Part I

ERNST T. KREBS, JR.*

Cancer arises through the differentiation of a cell in response to an organizer stimulus. This is fundamental. Spontaneous generation occurs nowhere in organic nature. The only means by which a new cell type can come into being is through the *differentiation* of a pre-existing undiffentiated cell. The degree of undifferentiation of such a cell may be partial or total. The more undifferentiated a cell is, the more primitive will be the immediate product of its differentiation. Thus the origin of the most primitive cell in the life-cycle is the result of the immediate differentiation of a totally undifferentiated cell, which for convenience we shall designate as the diploid totipotent cell.

The differentiation of a cell, and the persistence of the resultant differentiated cell, may bear either 1) a normal or 2) an anomalous relationship to the organism-as-a-whole. The anomaly may comprise a spatial one, a temporal one, or both. The cancer cell is a definitive cell, and like all other cells arises as the result of the differentiation of a less differentiated cell. Since no cell is spontaneously created, even the cancer cell has its normal counterpart in the life-cycle. In seeking this normal counterpart, it is logical to look for 1) that cell type whose spatial or temporal anomaly is invariably identified with cancer, and 2) that cell which, in normal spatial and temporal relationships, normally exhibits those properties which we identify as malignant.

It is, therefore, significant that the trophoblast cell is the only cell in the life-cycle that has *never* been observed outside of the canalization of pregnancy nor in the male at all except as cancer. Moreover, when the trophoblast cell has been so observed its exhibition has invariably comprised the most malignant exhibition of cancer known: chorionepithelioma. The *normal* pregnancy trophoblast cell possesses the following attributes of the cancer cell: autonomy, invasiveness, erosiveness, ability to metastasize, ability to destroy all non-trophoblast cells, and every other known property of the cancer cell. There is no property of the cancer cell that is not duplicated by the trophoblast cell. This is the most primitive cell in the life-cycle.

Just as the cancer cell has its normal counterpart in the life-cycle, so it arises 1) through a cellular mechanism normal to the life-cycle, and 2) in response to organizer stimuli normal to the life-cycle. Since the trophoblast cell or cancer cell is the most primitive cell in the life-cycle,

*John Beard Memorial Foundation, 642 Capp Street, San Francisco, California.

it arises through the differentiation of the most undifferentiated cell in the life-cycle: the diploid totipotent cell. The phenomenon of differentiation involved is that of meiosis (meiotic mitosis, heterotypic mitosis, or reduction division). The organizer stimulus involved is estrogen. In short, the emergence, persistence and death of cancer cells comprise phenomena having a complete and normal parallel within the life-cycle of every animal.

From these briefly outlined data we may derive an adequate definition of cancer:

Cancer is the expression of the spatially or temporally anomalous occurrence or persistence of trophoblast.

Primary Uterine Chorionepithelioma

Our understanding of the phenomenon of carcinogenesis will, perhaps, be facilitated if we first examine the single exhibition of cancer whose origin does not represent 1) a cellular differentiation anomalous to the organism-as-a-whole, 2) or trophoblast spatially or temporally abnormal in its relationship to the organism-as-a-whole. The single variable, then, that accounts for the malignancy of this exhibition of cancer is the *abnormal persistence of trophoblast*. Such an exhibition of cancer is primary uterine chorionepithelioma.

Trophoblast abnormally persists in primary uterine chorionepithelioma as a result of a deficiency in or lack of the humorally mediated factors that normally first check and then destroy the growing trophoblast of normal pregnancy. The degree of trophoblastic growth is conveniently determined through measuring, in the blood or urine, the specific hormone produced by the trophoblast cell: chorionic gonadotrophin. On the basis of such measurements, it has been established that it is impossible for the concentration of trophoblast that characterizes the early stages of gestation to persist throughout the span of gestation or post-partum without such persistence inevitably being exhibited as the most malignant of all possible exhibitions of malignancy. A *benign* hyperplasia of trophoblast simply can not occur. The inherent properties of trophoblast are "malignant," albeit normally canalized to physiological ends. An accentuation of these properties through a hyperplasia of trophoblast invariably results in their pathological expression.

The nature of the restraints against the over-proliferation of the trophoblast cells of normal pregnancy has been discussed in detail elsewhere.[2, 3]* It has, of course, been experimentally established that the removal of the pregnancy trophoblast from the uterus of the mother and its culture *in vitro* contiguous to non-trophoblast or somatic cells results in a fiercely malignant exhibition of the normal trophoblast.

---

*Pregnancy trophoblast may over-grow to *any* degree and the consequent exhibition may comprise anything from morning sickness, pre-eclampsia, and eclampsia to—usually in the absence of the foetus—hydatidiform mole and chorionepithelioma. These essentially successive states are generally exhibited with a progressive increase in the excretion of the hormone of the trophoblast cell—chorionic gonadotrophin (cf. 3).

Primary uterine chorionepithelioma was first described in 1895 by Marchand[4] who predicted that an elucidation of the pathogenesis of this exhibition of cancer would throw considerable illumination on the cancer problem as a whole. Though some workers, including Hubrecht[5] who first described the trophoblast cell in 18—, failed to recognize the fact that the trophoblast cells belong to the life-cycle of the conceptus, not that of the host, Marchand properly identified the trophoblast cells of chorionepithelioma with the life-cycle of the conceptus. Those who have not yet accepted the unitarian or trophoblastic thesis of cancer, point to primary uterine chorionepithelioma as being unique in that it represents the cancerization of the cells of the host by the cells belonging to a life-cycle genetically unique from that of the host. The trophoblastic or unitarian thesis, of course, recognizes that the constant malignant component, not only of primary uterine chorionepithelioma, but of all other exhibitions of cancer comprises trophoblast cells genetically unique from the life-cycle of the tissue they cancerize.

Primary uterine chorionepithelioma, the most malignant of all exhibitions of cancer, *involves only a single variable from the normal growth of pregnancy trophoblast.* This variable is *extrinsic* to the trophoblast and comprises loss of the ability of the host to resist the *normally* erosive, invasive and metastatic properties of the pregnancy trophoblast. Except to point out that maternal pancreatic dysfunction has been conclusively identified with the overgrowth of pregnancy trophoblast (cf. 3 for bibliography), we shall defer consideration of the humorally mediated factor that checks the growth of, and destroys, normal pregnancy trophoblast. Our examination, then, of the pathogenesis of primary uterine chorionepithelioma comprises a recapitulation of the established phenomena surrounding the development of the normal pregnancy trophoblast. It is axiomatic that the most virulent expression of a pathological process best typifies those phenomena unique to the process in all its exhibitions; therefore, the morphogenetic phenomena involved in the emergence of the normal pregnancy trophoblast of chorionepithelioma are, as we shall presently observe, applicable to all other and less malignant exhibitions of cancer.

Cellular Differentiation and Organizers. The emergence of every new cell type involves two essential factors: 1) the competent cell and 2) the organizer stimulus.

The competent cells from which normal pregnancy trophoblast arise are, of course, the diploid totipotent cells canalized in the gonads. The differentiation involved is meiosis whereby gametogenous cells are produced. The only alternative to the death of these cells is division. Normally this division occurs through fertilization, though such division may also readily occur parthenogenetically. In fact, Shapiro[6] and Pincus[7] have obtained apparently normal rabbits through the non-sexual activation to division of the haploid gametes of female rabbits, and Reimann & Miller[8]

have observed the commencing cleavage of the human ovum *in vitro* as a result of non-sexual activation.

The trophoblast cell in the normal canalization of pregnancy comes into being normally through sexual activation (fertilization). This comprises the union of two gametogenous cells and their subsequent division to produce trophoblast, though—as we have seen—the division of one gametogenous cell will suffice to produce trophoblast. Accordingly, the trophoblast cell of primary uterine chorionepithelioma comprises a cell that has arisen through sexual activation.

In primary testicular chorionepithelioma we find trophoblast cells identical in every ascertainable detail to those of primary uterine chorionepithelioma. These cells arise (like the trophoblast cells of the "parthenogenetic rabbit") through the non-sexual activation of an haploid gametogenous cell that has, in turn, arisen through the meiosis of a diploid totipotent cell.

The competent cell involved in the origin of normal pregnancy trophoblast, primary uterine chorionepithelioma, or testicular chorionepithelioma is, then, the diploid totipotent cell (in the gonads). The phenomena involved are those of differentiation: first, the unique differentiation of meiosis with the consequent production of an haploid gametogenous cell to produce trophoblast. The organizer stimulus involved is estrogen, which is produced by the granulosa, sustentacular and other somatic cells of the gonads in such contiguity to the diploid totipotent cells that a morphogenetically effective focal concentration of organizer is assured. The gradient of concentration of organizer (estrogen) is such that normally only a limited focus in the gonads receives effective organizer stimulus at one time.

It is noteworthy that the primary difference between the trophoblast of normal pregnancy and that of a primary testicular chorionepithelioma, for example, is that the former involves the meiosis of two diploid totipotent cells (one in the female and one in the male) and the production of two gametogenous cells which, upon union, divide to produce trophoblast; while the latter involves the meiosis of one diploid totipotent cell, the production of a gametogenous cell and the non-sexual division of this cell to produce trophoblast. This is congruent with the biological axiom that cells which are alike come from pre-existing cells that are alike.

We may summarize as follows: wherever a diploid totipotent cell occurs in the presence of a sufficient focal concentration of organizer, meiosis will occur with the consequent formation of a gametogenous cell and its division to produce trophoblast. Since cancer is the expression of the spatially or temporally abnormal occurrence or persistence of trophoblast, the abnormal persistence of such trophoblast will be exhibited malignantly. The degree of malignancy will vary directly with the concentration of the trophoblast and inversely with the concentration of somatic cells. It is clear, then, that cancer arises through cellular differentiation.

II.

Since *all* trophoblast comes into being normally through the organizer action of estrogen, it is instructive to consider the means by which estrogen production—hence trophoblast formation—may be inhibited. These are:

I. Gonadectomy (ovariectomy)
II. Hypophysectomy
III. Caloric restriction
IV. Adequate vitamin intake (especially B-complex)
V. Administration of testosterone
VI. Injection of chorionic gonadotrophin

On the other hand, hyperestrogenism—hence trophoblast production—may be encouraged through

I. Gonadectomy (orchidectomy)
II. Administration of anterior pituitary gonadotrophin
III. Administration of natural estrogens
IV. Administration of synthetic estrogens
V. Granulosa-cell tumors
VI. Adrenocortical hyperplasia (consequent to gonadectomy)
VII. Failure in the detoxification of estrogen
  (a) vitamin deficiency (especially of B-complex)
  (b) protein inadequacy
  (c) cellular toxins
VIII. Hepatic cirrhosis
IX. Experimental damage to liver and the reticulo-endothelial system in general
X. Endocrine imbalance consequent to
  (a) surgical ablation of endocrine tissue
  (b) roentgen irradiation
  (c) ectopic position of sex glands
  (d) synthetic augmentators of sex hormones
    (1) hematoporphyrins for estrogen
    (2) zinc salts, etc., for pituitary gonadotrophin (FSH)
    (3) ultra-violet radiation

The function of estrogen is two-fold: 1) induction of meiosis in canalized diploid totipotent cells, and 2) preparation of the soma for reproduction. The latter involves the development of the mammary glands and uterus in particular and the secondary sex characteristics in general. In the male estrogen is concerned with the induction of meiosis in the diploid totipotent cells of the seminiferous epithelium, but the secondary sex characteristics are here dependent primarily upon the organizer effect of testosterone. Testosterone, like progesterone, strongly inhibits the meiosis of the diploid totipotent cells both in the male and in the female. Since the common denominator of all these effects is cellular differentiation in response to an organizer stimulus, it is noteworthy that: 1) estrogen induces the meiosis of diploid totipotent cells as well as the differentiation of somatic cells, while 2) testosterone also causes the differentiation of somatic

cells in the development of secondary sex characteristics; but not only fails to induce the meiosis of diploid totipotent cells, but inhibits the effect of estrogen in such induction as well.

Since the most malignant of all exhibitions of cancer clearly comprises frank trophoblast cells that arise through the meiosis of a diploid totipotent cell in response to the specific organizer stimulus of estrogen, it is obvious that anything which facilitates the production and persistence of estrogen will encourage the production of trophoblast, and anything which inhibits the production of estrogen or suppresses its action will inhibit the production of trophoblast. Testosterone, progesterone, chorionic gonadotrophin (but not pituitary) are the chief hormones that inhibit estrogen and, therefore, the possible production of trophoblast. In brief, primary uterine chorionepithelioma can not occur within an organism lacking sufficient estrogen to cause an ovarian diploid totipotent cell to undergo meiosis; and testosterone, progesterone, and chorionic gonadotrophin are hormones which will inhibit the meiosis of a diploid totipotent cell. With the most malignant exhibition of cancer as our referent, we shall examine the applicability of these data to the genesis of less malignant exhibitions of cancer.

If cancer is an unitarian phenomenon and thereby trophoblastic, it follows that the malignant component in all exhibitions of cancer: 1) comprises the same cell type that comprises the most malignant exhibition of cancer—primary uterine chorionepithelioma, 2) shares the same cellular origin, 3) comes into being through the same cellular phenomena, 4) is susceptible to induction through the same organizer stimuli, and 5) is amenable to destruction by the same antithetic factors.

Just as the cancer cell has its normal counterpart in the pregnancy trophoblast of the life-cycle, so it also has its normal organizer—the means of its evocation or differentiation—in the life-cycle. This organizer factor is estrogen. In addition to the normally occurring estrogen, there are various synthetic compounds that duplicate the effect of natural estrogen (in varying degrees). Some of these compounds appear more active than natural estrogen and are excreted with greater difficulty. This because, in the process of natural selection, the organism could make no specific provision for the detoxification of such synthetic substances.

We shall first consider the role of natural or endogenous estrogen in carcinogenesis before turning to that of the synthetic compound.

Estrogen as a Carcinogen

A carcinogen is defined as any substance or agent, chemical or physical, which when present under certain conditions is followed by the appearance of tumors which would not have appeared otherwise[2].

Within the meaning of this definition, *normally occurring* or endogenous estrogen is clearly the universal carcinogen. As we shall observe from direct experimental evidence in laboratory animals, and from indirectly adduced clinical evidence in man, normally occurring estrogen is the only

carcinogen in the environment of either man or animals for which a certain causal relationship can be demonstrated in all the known exhibitions of cancer from primary uterine chorionepithelioma to the leukemias.

Within the context of the unitarian or trophoblastic thesis, the carcinogenic effect of estrogen comprises specifically its normal organizer effect in inducing the meiosis of a diploid totipotent cell with the consequent production of a gametogenous cell that upon division results in "the spatially or temporally abnormal occurrence or persistence of trophoblast." Correlatively, then, carcinogenesis represents the spatially or temporally anomalous recapitulation of phenomena normal to the life-cycle.

Estrogen and Trophoblast Growth. Although a reasonable systematization in the study of the role of estrogen in carcinogenesis requires that we defer here a detailed examination of the means by which pregnancy trophoblast is normally inhibited and then destroyed in the span of gestation, and the role that estrogen plays in the partial inhibition of the humorally mediated factors antithetic to trophoblast, it is necessary to an intelligent continuity of the subject to examine here the effect of estrogen in facilitating the implantation of pregnancy trophoblast without so inhibiting the humorally mediated factors antithetic to the trophoblast as to cause the overgrowth of the trophoblast as primary uterine chorionepithelioma.

Though estrogen depresses the humorally mediated antithesis to the trophoblast, the self-limiting nature of this mechanism is demonstrated in the fact that estrogen also inhibits the aggression of cellular trophoblast (cytotrophoblast) through forcing its conversion to the less malignantly exhibited syncytial state. This is demonstrated in the depression in the production of trophoblast-cell-produced chorionic gonadotrophin that follows the administration of *either* estrogen or testosterone in normal pregnancy.[10, 11] Kullander,[12] and later Hinglais & Hinglais,[13] reported impressive clinical remissions in primary uterine chorionepithelioma through the administration of massive doses of estrogen. The degree of these steroid-induced remissions bore a quantitative relationship to the depression in the excretion curve of chorionic gonadotrophin. The reason that such estrogen therapy did not permanently resolve the chorionepitheliomatous overgrowth of the pregnancy trophoblast was that the primary deficiency in somatic factors antithetic to the trophoblast was too profound to destroy even the syncytial trophoblast induced by estrogen administration. Had this primary deficiency extrinsic to the trophoblast not been so great, a chorionepitheliomatous overgrowth would not have occurred in the first place; because an adequate concentration of the antithetic humoral factors induce the defensive conversion of the aggressive cytotrophoblast to the steroid-producing syncytial state. The steroids thereby produced further inhibit the cytotrophoblast—just as the artificially administered steroids do.

The lability of this mechanism and its quantitative nature are illustrated in the not infrequently seen resolution of the metastases of primary uterine chorionepithelioma following the removal of the primary

growth.[14, 15, 16, 17] It is, indeed, significant that the most malignant exhibition of cancer exhibits the greatest tendency to spontaneous remission.

Finally, the question logically arises as to why estrogen and/or testosterone, which inhibit the growth of normal pregnancy trophoblast and prevent its chorionepitheliomatous overgrowth, do not also inhibit and thereby prove palliative to all exhibitions of cancer—if all have trophoblast as their constant malignant component. For such palliation to occur, localization of the sex steroids at the affected lesion is prerequisite. The somatic cells of the prostate and mammary gland both localize the sex steroids; therefore, these steroids are palliative to the malignant exhibition of such tissues. The use of the physiologically antagonistic steroid is rational since it has the advantage of causing a physiological atrophy of the affected target organ. The seemingly paradoxical nature of the palliative effect[17, 18] of massive doses of estrogen in mammary cancer is explicable in the fact that estrogen also inhibits the growth of canalized or pregnancy trophoblast. The hyperplasia that estrogen causes in mammary tissue involves the somatic cells, not the autonomous malignant component or trophoblast which is inhibited by either estrogen or testosterone.

We may summarize as follows: 1) estrogen causes the meiosis of diploid totipotent cells, and 2) facilitates the consequent development of trophoblast through normally depressing host factors antithetic to trophoblast. Carcinogenesis is achieved when the latter depression becomes such as to permit the anomalous occurrence or persistence of trophoblast. *Anything* that will duplicate these effects of estrogen will prove carcinogenic.

Carcinogenic Effects of Estrogen. The role of estrogen in the genesis of mammary cancer in mice was adumbrated in the demonstration by Lathrop & Loeb[19] in 1913 of the increased incidence of mammary tumors in breeding mice. This observation and the fact that spontaneous mammary tumors are very rare in male mice, led these workers[20] in 1916 to investigate the effect of ovariectomy at an early age on the incidence of mammary tumors in mice. It was found that castration resulted in a remarkable decrease in the incidence of spontaneous mammary cancer. Cori[21, 22] confirmed these findings in his observation that early castration reduced the incidence of such tumors from 78.5% found in intact animals to 0% in the castrates. Murray[23, 24, 25] made similar observations.

In 1928 Murray[26] implanted ovaries into castrated male mice of a strain in which the females have a high incidence of spontaneous mammary cancer and obtained mammary tumors in a number of these mice. Jongh & Korteweg[27] confirmed these findings. With the isolation of chemically pure estrogen, Lacassagne[28] in 1932 induced mammary cancer in female mice given weekly injections of 30 micrograms of folliculin benzoate in oil. Further studies confirmed the fact that the administration of estrogen in males or in non-breeding females induces mammary cancer to the same degree as these tumors occur spontaneously in breeding females of the same strain.[29, 30, 31]

While hypophysectomy has the same effect as ovariectomy in decreas-

ing the incidence of spontaneous mammary tumors in mice, the transplantation of anterior lobe tissue increases the incidence of mammary tumors in mice of certain strains, but such transplants are ineffective following ovariectomy.[32, 33] Spontaneous uterine cancer is relatively rare in all strains of mice, but a high incidence of invasive lesions of the cervical epithelium arose in estrogen-treated mice.[34] Although most intact and adequately fed experimental animals possess a normal capacity to detoxify estrogen, the susceptibility to the estrogen-induction of mammary cancer is enhanced in some mice by a transmissible milk factor;[35, 36, 37, 38] hence, it is of interest that in the rabbit, which is not susceptible to the milk factor, spontaneous mammary[39] and uterine cancer[40] were reported in those animals that at some time had toxemia of pregnancy and thereby acquired a hepatic impairment in the detoxification of estrogen. And in rats, which normally lack the milk factor, the artificial administration of estrogen produces mammary cancer in some strains;[41] moreover, estrogen has also produced mammary cancer in mice lacking the milk factor.[42] On the other hand, the milk factor is not carcinogenic in the absence of estrogen.[43]

The mammary glands, uterus, lymphoid tissue, testes, prostate, hypophysis, and skeletal system are, to one degree or another, target-organs for normally occurring estrogen. It is not, therefore, surprising that—with the possible exception of the undetermined status of the prostate—estrogen is responsible for the induction of cancer in these tissues with a frequency that varies roughly with the degree to which the tissue is a physiological target for normal estrogen. This correlation is consistent with the fact that the organizer or morphogenetic effect of estrogen on normally canalized diploid totipotent cells depends upon a high focal concentration of the steroid. For example, not all diploid totipotent cells within the gonads undergo meiosis at once: those closest to the highest concentration of estrogen are first to undergo meiosis—in the presence of equal susceptibility or competence on the part of the cells. So it is with the extra-gonadal diploid totipotent cells.

Lymphoid tissue is relatively susceptible to the selective action of estrogen, which means a selective ability to concentrate estrogen. The incidence of leukemia was higher among females than among males of certain leukemia-susceptible stocks,[44] but was reduced by ovariectomy.[45] Since castration results in an increase of estrogen in the male, it is not unexpected that castrated males had a higher incidence of leukemia than did controls, though the injection of testosterone reduced the incidence to about the same level as in intact males.[46]

Leukemogenesis. According to the trophoblastic or unitarian thesis, leukemia is the result of the development of trophoblast in lymphoid or medullary tissue. The leukemic exhibition is primarily the expression of the proliferation of *somatic* white blood cells of various degrees of maturity. This is why the most malignant leukemias (so-called aleukemic leukemias) are frequently associated with an actual leukopoenia, just as not infrequently other highly malignant exhibitions of cancer are associated with

relatively slight primary tumefaction. Lymphoid or medullary tissue does not always respond to the presence of trophoblast with a leukemic exhibition; sometimes a sessile lymphoid tumor or a chloroma is formed. These are frequently associated with a leukemic exhibition. Estrogen induces lymphoid tumors in certain strains of mice.[47, 48, 49] The simultaneous administration of testosterone propionate with estrogen almost completely inhibits the leukemogenic action of estrogen.[50]

The skeletal system also has a pronounced capacity to concentrate steroids. The vitamin D steroids, as well as estrogen, act as organizers to induce ossification. Female mice of one strain showed a 75% incidence of bone tumors; the males a 25% incidence.[51, 52] The administration of estrogen increased the incidence of bone tumors in males and decreased the age at which they appeared in both sexes.[53] The direct implantation of estrogen into the medullary cavity of mice also resulted in bone tumors.[54]

The testes are normally invoved in estrogen metabolism. It is interesting, therefore, that the administration of estrogen (either triphenylethylene, estradiol benzoate or stilbestrol) results in a high incidence of testicular tumors in strain A mice.[51] Lacassagne observed that the administration of estrogen induced lymphosarcomas and uterine tumors as well as mammary tumors in mice.[52] Hypophyseal tumors have also been reported in estrogen-treated mice,[53] and skin cancers have been produced by the subcutaneous injection of estrogen.[54]

We have examined first the relatively simplified, or direct, conditions under which the apposition of normally occurring organizer (estrogen) and competent cell (diploid totipotent cell) may be achieved or averted. Ovariectomy, the transplantation of ovarian tissue, the injection of estrogen, the elicitation of increased endogenous estrogen through the endocrine shift consequent to castration in the male, the neutralization of estrogen by testosterone or progesterone, hypophysectomy, the implantation of hypophyseal tissue—all of these technics are relatively simple and direct methods of increasing or decreasing the estrogenic stimulus to an organism.

More recently Wooley & Little[55] observed that in certain inbred strains of mice (C_3H and dba) castration not only failed to prevent the normal development of the mammary glands, but also failed to prevent the subsequent development of mammary cancer. In examining the effect of early gonadectomy on C_{57} Black strain and on ce strain, both of which have a low spontaneous incidence of mammary cancer, these authors found that while the gonadectomized C_{57} strain failed to show normal mammary gland development and failed to develop mammary cancer, the castrated ce strain mice showed both normal mammary gland development and subsequently a relatively high incidence of mammary cancer.

At first glance these findings appeared to contradict the thesis that estrogen is the sole normally occurring determiner of mammary tumor formation. But this contradiction was readily resolved when the effects of gonadectomy on the development of the adrenal cortex in each strain were observed. In those strains of mice, dba and C_3H, showing normal

mammary gland development plus a high incidence of spontaneous mammary carcinoma *after* gonadectomy, a pronounced benign hyperplasia of the adrenal cortex was observed. While the C_{57} Black strain, which failed to show normal mammary gland development and failed to develop mammary cancer after gonadectomy, showed only mild adrenocortical hyperplasia after gonadectomy, the compensatory adrenocortical hyperplasia in the gonadectomized mice of ce strain was found to be so intense in both sexes that adrenocortical carcinoma developed in 100% of the ce strain mice, though the malignant change appeared first in the female.

With the removal of the gonads, there is a compensatory outpouring of adrenocorticotrophic hormone from the anterior pituitary. As a result the adrenal cortices commence the compensatory production of estrogen. Those gonadectomized female mice, for example, which developed adrenocortical carcinoma exhibited continuously after such development pronounced estrogenic reactions. Mice of the ce strain do not spontaneously develop adrenocortical carcinoma.

The estrogen compensatorily produced by the functional hyperplasia of the adrenocortical tissue in strain ce mice was not only sufficient to develop and maintain the mammary glands, as well as to bring about a malignant induction in a considerable number of them, but it was also sufficient to bring about a malignant induction in the normal cortices of 100% of these gonadectomized ce strain mice. In the induction of both the adrenocortical carcinoma* and the mammary carcinoma, the mechanism involved: 1) the conjunction of an adequate focal concentration of estrogen and a diploid totipotent cell, 2) the meiosis of the diploid totipotent cell, 3) the consequent production of ectopic trophoblast, and 4) the continuing secretion of a sufficient quantity of estrogen to depress the humorally mediated somatic factors normally antithetic to trophoblast.

It is important to note that hyperplasia in itself is not conducive to malignant induction. Were this the case, every hypertrophic thyroid and every uterine fibromyoma would be malignant. It is true, however, that the hyperplasia induced through estrogen (and through carcinogenic steroids) is much more susceptible to malignant induction than that hyperplasia unassociated with either estrogen or compounds duplicating the action of estrogen. Estrogen, or a similar compound, is required to elicit meiosis in the diploid totipotent cell; to prepare a congenial decidua for the malignant process; and, not least important, to condition the organism for the toleration of trophoblast. The latter factor is undoubtedly the most important in contributing to the comparatively great latency associated with ordinary malignant induction, since there are only two fundamental cell changes which separate the benign diploid totipotent cell from the trophoblast: 1) meiosis, and 2) division of the resultant gametogenous cell. These two changes occur almost simultaneously.

*The adrenal cortex and the gonad arise from a common primordium, and develop contiguously during the period in which the terminal epithelium receives its complement of diploid totipotent cells. As a result there is also a high concentration of such cells received by the contiguous adrenal tissue, as comparative studies have shown.

That conditioning of the organism for the toleration of the spatially aberrant trophoblast involves most of the latency in malignant induction is further suggested by the fact that primary uterine chorionepithelioma, occurring in the presence of *pre-existing* normal trophoblast, may develop and destroy the patient in the course of a few weeks.[51, 52] It is further significant that the incidence of this exhibition of cancer is approximately the same as that of all other exhibitions of cancer in women of the same age group.[53] Because the trophoblast belongs to the life-cycle of the foetus, its chorionepitheliomatous overgrowth, correlative to the incidence of all other cancers in the host, clearly indicates not only that the trophoblastic overgrowth resides in an infirmity intrinsic to the host, but also that such a host deficiency is correlative to the genesis of *all* exhibitions of cancer sustained by the host.

Caloric Restriction. Tannenbaum[54] points out that it is now well established that a caloric restriction of the diet to about 2/3 of what a mouse would eat if fed *ad libitum* effects a significant reduction in spontaneous breast tumors, primary lung tumors, induced carcinomas, induced sarcomas, and leukemia.[55, 56] In 51 full-fed C_3H mice 67% developed mammary adenocarcinoma while no tumors appeared in 44 mice on the restricted diet.[57] Underfeeding resulted in the reduction of spontaneous leukemia from 65 to 10.1% in mice.[58] A 50% reduction in calories, without reduction in the amount of dietary essentials, reduced the incidence of mammary tumors from 100% to 12.5% in virgin mice, and to 18.5% in breeding mice.[58]

Chronically underfed rats and mice will cease to have estrus.[59] Because the effects of prolonged underfeeding resemble hypophysectomy, Mulinos & Pomerantz[60] have applied the term "pseudo-hypophysectomy" to the pituitary status in chronically underfed rats. Other investigators have demonstrated that caloric restriction leads to atrophic changes in the glands of internal secretion.[61, 62, 63] The implantation of estrogen pellets in such animals results in growth of the mammary tissue and initiation of continuous estrus with a considerable rise in tumor incidence.[64, 65] As in the case of the reduced incidence of tumors or leukemia following ovariectomy, the earlier caloric restriction is instituted in the experimental animals the greater the reduction in the incidence of all tumors.[66]

Greenstein[67] has succinctly summarized the role of dietary restriction in cancer: "The dietary regimes devised to date which effectively prevent the appearance of tumors in experimental animals are for the most part those which abolish estrus and capacity for breeding."

The same factors which, in abolishing "estrus and the capacity for breeding," prevent or retard the appearance of canalized pregnancy trophoblast—hence the possibility of primary uterine chorionepithelioma—invariably prevent or retard the appearance of all other exhibitions of cancer. This is because precisely the same phenomena are involved in the production of normal pregnancy trophoblast as are involved in the production of the constant malignant component in all exhibitions of cancer. All exhibitions of cancer, other than primary uterine chorionepithelioma, come into being through the spatially aberrant differentiation of a diploid totipotent cell existing outside the normal canalization of reproduction. When such

ectopic trophoblast expresses its *normal* properties—attempting to do precisely what it does in its normal canalization of reproduction—the resulting exhibition is invariably a malignant one. The degree of malignancy varies directly with the concentration of ectopic trophoblast cells, which varies with the degree to which the soma resists or morphologically masks the ectopic trophoblast; hence the most malignant exhibition of extra-genital cancer possible is the relatively rare primary extra-genital chorionepithelioma (identical with that of the primary uterine and testicular forms) in which somatic resistance to the ectopic trophoblast is so inadequate that the trophoblast cells are frankly exhibited as such. This is the most malignant exhibition of cancer possible since it is comprised almost totally of frank trophoblast cells.

These trophoblast cells normally come into being through the organizer effect of estrogen. Without trophoblast cells there can be no primary uterine chorionepithelioma or any less malignant exhibition of cancer. Though the unitarian thesis recognizes that the constant malignant component in *all* exhibitions of cancer is brought into being through phenomena that typify the most malignant exhibition, those who do not yet accept the unitarian nature of cancer might object that there could be only a fortuitous association between the ability of the estrogen molecule normally to induce meiosis, and thereby ultimately trophoblast, and the same molecule to evoke nonchorionepitheliomatous exhibitions of cancer. In reviewing the pronounced variations in the chemical configurations of synthetic estrogens, Stern & Willheim[68] wrote:

> "These observations are especially significant in view of the fact that the chemical configuration of these substances (synthetic estrogens) differs essentially from that of natural estrogen, and hence it must be *deduced that the biological effects evoked by these substances, and not their chemical nature, primarily determine their carcinogenic activity.*" (Italics by E. T. Krebs)

Progesterone and testosterone not only are incapable of inducing the specialized differentiation comprising the meiosis of a diploid totipotent cell, but both serve to inhibit the action of estrogen in inducing such meiosis. Billing & Hamilton[70] suppressed meiosis and the associated follicular development and ovulation in guinea pigs for a period of nine months through the daily administration of testosterone propionate. The reproductive cycle and ovulation returned soon after cessation of androgen injections and some animals bore and raised young. The inhibiting effect of testosterone on the meiosis of the diploid totipotent cells of the seminiferous tubules accounts, of course, for the pro-sterility effect of this hormone. Chorionic gonadotrophin is also highly effective in suppressing meiosis of diploid totipotent cells.

If the carcinogenic effect of estrogen comprises its normal capacity to induce meiosis in diploid totipotent cells, which capacity is partly or completely inhibited through the action of testosterone, it follows that if the genesis of the cancer cell involves the action of estrogen in inducing the meiosis of a diploid totipotent cell—however spatially aberrant the

differentiation involved—then such meiosis should logically be inhibited by the specific hormones which are known to inhibit the meiosis of diploid totipotent cells. Lacassagne & Raynaud[71] administered testosterone propionate in biweekly injections to young female mice of a highly susceptible strain, beginning a few days after birth and continuing throughout the life of the animals, and noted that none developed mammary tumors. Nathanson & Anderson,[72] Jones[73] and Heiman[74] showed that testosterone lowered the incidence of spontaneous mammary cancer in mice whether virgin or bred. Miller & Pybus[75] found that the incidence of tumors in estrogenized castrate male mice was twice as great as in estrogenized intact males. Within the purview of the unitarian thesis, it is particularly significant that the action of testosterone is one of impeding the induction of malignancy; tumors once developed are unaffected by the hormone.[72, 73, 74] Nor is the persistence of the inductive agent ever necessary for the continuing growth or survival[75, 76, 77] of the tumor; however a tumor may start, it ends by presenting properties in common with other tumors. The pathway through which the organizer is mediated does not influence the malignant exhibition produced.

The means by which the apposition of competent cell (diploid totipotent cell) and effective concentration of organizer (estrogen) may be achieved are highly diverse. This diversity is especially apparent in the mediation of the effect of exogenous carcinogens, and in the factors which augment or depress that effect. At first glance the problem of carcinogenesis may appear hopelessly complex in view of the diversity of the pathways by which the organizer stimulus may be mediated, but as we examine the subject further in the light of the unitarian or trophoblastic thesis, we find a remarkable orderliness characterizing it. Although the role of estrogen may not always be immediately apparent, and though it may be obscured in the sometimes devious pathways by which estrogenic effect is mediated, the fact remains that estrogen is the only endogenously occurring factor conclusively identified with the immediate genesis of cancer in man and animals. Moreover, the carcinogenic effect of estrogen has been identified in the genesis of practically every exhibition of cancer in experimental animals—from mammary, cervical and uterine adenocarcinoma to testicular growths and leukemia.

Despite an intensive and continuing search for possible endogenous carcinogens in normal or cancer tissue, nothing tangible has been uncovered. Some have, for example, speculated that desoxycholic acid, a bile acid, might be fortuitously converted to the powerful carcinogenic methylcholanthrene as a result of disturbed metabolism.[78, 79] There is, however, no evidence whatever that this ever occurs. It is worthy of note that the carcinogenicity of estrogen is not dependent upon any aberrant metabolite of this compound, but upon the normal estrogen in its active state. Several workers have succeeded in extracting from the liver of non-cancer[80] as well as cancer patients[81] a fat-soluble tarry substance carcinogenic in certain experimental animals. Since the liver is the main

organ for the detoxification of such steroids as estrogen, it would be surprising, indeed, if the extraction of liver with fat solvents consistently failed to yield material with some carcinogenic potency.

The substantial period of latency in malignant induction must be equated with the possible carcinogenicity of endogenous compounds. Estrogen is the only endogenous compound of demonstrated carcinogenicity; and, equally important, it is a compound that may be present in sufficient and sustained concentration for a period fully satisfying the requirement of latency.

It is not possible here to review fully the comprehensive literature on the proved carcinogenicity of estrogen in experimental animals and in man. The need for such is mitigated in the fact that there is simply no evidence for the existence of any endogenously occurring carcinogen other than estrogen.

A single example will suffice as a concluding demonstration of the devious ways in which the carcinogenicity of estrogen may be mediated. Furth & Butterworth[81] (cf. Furth & Furth[82]) observed that one-fourth of a number of mice irradiated with 400 r of roentgen ray developed granulosa-cell tumors of the ovary. Although the incidence of spontaneous mammary carcinoma is normally 17% in the unirradiated mice of this strain, only 2.7% of the irradiated animals that did not develop granulosa-cell tumors developed mammary cancer. On the other hand, of the mice that developed granulosa-cell tumors, 28.6% also developed mammary cancer. Since irradiation itself reduced the incidence of breast cancer sevenfold in mice not developing estrogen-producing or granulosa-cell tumors, and increased the incidence tenfold in those developing such tumors, the carcinogenic role of estrogen appears clear here*. Uterine cancers are also sequential to granulosa-cell tumors. The development of the latter is the result of a specific endocrine imbalance. Levine & Witschi[83] found that when female rats were sterilized and placed in parabiotic union with normal females the latter went into constant estrus as a result of the compensatory excess of gonadotrophin from the castrate. Li & Gardner[84, 85] demonstrated that the intrasplenic isolation of ovarian tissue in castrate male and female mice shunted the ovarian estrogen to the hepatic detoxification system before the estrogen could reciprocally inhibit the anterior pituitary. As a result of the consequently unchecked outpouring of pituitary gonadotrophin and the excessive stimulation of the ovarian target in the spleen, granulosa-cell tumors and luteomas were produced in the excessively stimulated ovarian tissue. Essentially, the same phenomena were involved in the induction of adrenocortical carcinoma in 100% of the castrated males and females of the ce strain of mice.

*Novak reported three girls under seven years of age in whom granulosa-cell tumors had induced precocious puberty exhibited in an acceleration of skeletal growth, mammary hypertrophy, the appearance of axillary and pubic hair, and hypertrophy of the external sex organs. These cases illustrate the action of estrogen as an *organizer* or a *morphogenetic hormone* in inducing cellular differentiation. The carcinogenic effect of estrogen is confined to the spatially aberrant induction of differentiation in a diploid totipotent cell—which is, after all, the end to which all these other estrogen-induced phenomena are subservient in the normal reproductive canalization.

A similar situation is found in cryptorchids. Hamilton & Gilbert[88] have reported the incidence of testicular cancer as 50 times greater in human cryptorchids than in normal subjects. Others have reported figures as high as 100 times greater. The urine of cryptorchids is characterized by a pronounced excess of estrogen-evoking gonadotrophin, since the interstitial cells of the undescended gland do not produce enough testosterone reciprocally to inhibit the outpouring of anterior pituitary gonadotrophin. The removal of one gonad in birds frequently results in a malignant change in the remaining gonad as a result of the increased pituitary output of estrogen-evoking gonadotrophin. The induction of testicular cancer in fowls through the injection of zinc salts is adumbrated by the following facts: 1) such salts increase by eightfold the specific estrogen-evoking activity of anterior pituitary gonadotrophin, 2) the malignant change occurs normally only during the reproductive season, but 3) it may be induced at any season if an injection of anterior pituitary gonadotrophin accompanies the injection of zinc salts. Significantly, chorionic gonadotrophin proved non-carcinogenic with the zinc salts, and the use of materials equally irritating as the zinc salts failed to induce cancer if they did not show an augmentative effect on the action of pituitary gonadotrophin.

Greulich & Burford[87] reported three examples of testicular tumors in cryptorchid dogs. In all cases the dogs showed estrogenic responses of the mammae and were sexually attractive to male dogs. That a pathological excess of estrogen should be associated with cancer in these dogs is especially significant since, as Greenstein reported in 1947, "No one has yet succeeded in definitely inducing tumors in dogs by the administration of any of the polycyclic hydrocarbons." All vertebrates are susceptible to the carcinogenic effect of estrogen, which is truly the universal carcinogen because of its organizer effect in inducing meiosis in diploid totipotent cells.

Within the context of the unitarian or trophoblastic thesis, endocrine imbalance has a very specific meaning in the etiology of cancer. This imbalance involves specifically a preponderance of active estrogen, which is the organizer responsible for the meiosis of a diploid totipotent cell. Whether the consequent trophoblast persists or perishes depends upon the extent to which the estrogen has succeeded in depressing the mechanism by which trophoblast is normally destroyed.

Although the clinical literature does not clearly disclose an association between mammary cancer in women and granulosa-cell tumors, it does disclose a definite association between granulosa-cell tumors and adenocarcinoma of the uterus—another target organ for estrogen. In view of the relative scarcity of these ovarian tumors, it is hardly conceivable that their association with endometrial cancer, as reported by Schroeder,[88] Stohr,[89] Dockerty,[90] Russell[91] and Taylor & Greeley[92] was a mere coincidence. Daniels & Babes[93] reported histological evidence of ovarian overfunctioning in most of the ovaries removed from 35 patients with uterine cancer. In a sampling derived from over 2,000 cases of ovarian tumors,

Herrell[94] found that ovariectomy prior to the onset of breast cancer reduced its incidence tenfold. Olch,[95] Crossen[96] and Emge[97] report that women coming to the menopause early have an appreciably lower incidence of mammary cancer than those in whom there is a later cessation of ovarian estrogen production. An abnormally high level of estrogen has been reported in patients with uterine tumors.[98, 99]

In the following pages we shall consider briefly the role of estrogen in carcinogenesis as it is modified by 1) the additive effect of carcinogenic polycyclic hydrocarbons, 2) nutritional factors, and 3) efficiency of the detoxification mechanism.

III.

Carcinogenic Polycyclic Hydrocarbons

All carcinogens may properly be classified into one of the following groups:

I. Normally occurring estrogen

II. Substances that duplicate the specific morphogenetic (carcinogenic) effect of normally occurring estrogen.

Ancillary to these two groups of carcinogens are:

III. Factors which inhibit the detoxification of normally occurring estrogens—and thereby of those substances that duplicate the effect of normally occurring estrogen

IV. Factors or substances that elicit estrogen or augment the morphogenetic effect of estrogen

V. Factors or substances which inhibit the morphogenetic (carcinogenic) action of estrogen—and thereby of those substances specifically duplicating the morphogenetic (carcinogenic) action of estrogen.

In Group I belong all endogenous estrogens—those arising from the ovaries, testes, and adrenal cortices; in Group II, the classical polycyclic hydrocarbons; and in Group III, such pro-carcinogenic factors that impair the steroid detoxification system as arsenic, the azo dyes, beryllium, carbon tetrachloride, chloroform, parasites, etc. In Group IV are anterior pituitary gonadotrophin and adrenocorticotrophic hormone as the elicitors of estrogen from the gonads and adrenal cortices, respectively. In this group there are also the augmentors of gonadotrophic action, such as the zinc and copper salts. These result in an augmentation of the estrogenic effect. There are also in Group IV the direct augmentors of estrogenic activity such as hematoporphyrin. In Group V we find such inhibitors of estrogen (or its morphogenetically duplicative analogues) as testosterone and progesterone.

The true carcinogens of Groups I and II are characterized by the following properties: 1) they are not organ- or tissue-specific, but act wherever they are presented to the competent cell in a sufficient concentration; and 2) though other factors—milk-factors, viruses, other true carcinogens—may contribute in some cases a highly additive effect, these other factors are not indispensable. On the other hand, factors in Groups III and IV are selectively carcinogenic against certain tissues or organs

and require the mediation of either estrogen or the true exogenous carcinogens (Group II). Probably the specific or ultimate experimental criterion for this classification is the action of the respective substances against tissue culture preparations from which the variables presented by the complexity of the organism are absent.

The hormone-like action of the estrogens in their induction of cancer is demonstrated by the fact that the carcinogenic effect is produced by the relatively low concentrations in which estrogen endogenously occurs. Like the endogenous estrogens, the carcinogenic polycyclic hydrocarbons are capable of acting in extremely small concentrations. This group of compounds is typified by 3, 4 benzpyrene, 1, 2, 5, 6-dibenzanthracene, and 20-methylcholanthrene. Shear[100] was able to elicit a subcutaneous carcinoma in a mouse with less than 0.0004 milligrams of 1, 2, 5, 6-dibenzanthracene in cholesterol. The originally studied carcinogenic tar did not contain more than 0.003% carcinogenic hydrocarbon in the form of 3, 4-benzpyrene.[101] Andervont[102] demonstrated a similar effectiveness for methylcholanthrene and 1, 2, 5, 6-dibenzanthracene in low concentrations.

In 1913 Loeb and his coworkers recognized the carcinogenic effect of an ovarian factor that was later to be isolated and identified as estrogen. Two years later in 1915 Yamagiwa & Itchikawa[103, 104, 105] proved the carcinogenic effect of tar, which effect was later identified with benzpyrene. Early in the 1930's the structural formulae for both estrogen and the carcinogenic polycyclic hydrocarbons were determined. As early as 1933 Cook & Dodds[106] described the estrogenic effect of 3, 4-benzpyrene, the original carcinogen of tar, and of two derivatives of benzanthracene in the elicitation of vaginal cornification in mice. Lewis & Turner[107] observed that 1, 2, 5, 6-dibenzanthracene exerted a pronounced estrogenic effect on the mammary tissue of male mice. Perry[108] observed vaginal cornification in spayed mice following the injection of 3, 4-benzpyrene. A number of workers have shown that methylcholanthrene serves as estrogen does in more susceptible strains of mice.[109-114] Methylcholanthrene, however, induces mammary tumors in males only if estrogen is simultaneously administered. This typifies the additive effect of estrogen and the carcinogenic polycyclic hydrocarbons.

Had the endocrinologist first studied the pharmacological properties of tar, 3, 4-benzpyrene, or 1, 2, 5, 6-dibenzanthracene, he would have properly described these compounds as estrogens. On the other hand, as early as 1913 Loeb identified the effect of estrogen as carcinogenic.

We have previously observed how testosterone inhibits the meiosis of canalized diploid totipotent cells and how it decreases fertility and the incidence of spontaneous and induced mammary cancers in mice. Flaks & Ber[115] have reported that testosterone delays the induction of tumors in mice painted with methylcholanthrene. Just as chorionic gonadotrophin will act to inhibit meiosis in the diploid totipotent cells in the female through the elicitation of progesterone and in the male through the elicitation of testosterone, so chorionic gonadotrophin is reported to decrease the susceptibility of hepatic tissue to azo dye-induced cancer[116] as well as to

tar-induced cancer of the skin.[117] Andervont, Grady & Edwards[118] report that testosterone increases the resistance of mice to the induction of hepatic cancer with o-aminoazotoluene. Andervont & Dunn[119] have made similar observations in hepatic cancer in mice.

Carcinogenic Hydrocarbons as Organizers. As a result of their observations on the effect of estrogen and the carcinogenic polycyclic hydrocarbons in the experimental induction of primitive embryonic tissue to various differentiated structures, Waddington[120] and Needham[121, 122] grouped these substances with other "evocators" or "organizers" capable of inducing such effects as the neuralization of primitive ectoderm. While these morphogenetic effects are derived from a substratum of highly undifferentiated or multipotent cells, the induction of cancer involves the differentiation of totally undifferentiated cells. A diploid totipotent cell is a cell that "has not entered into body-building," as Arey phrases it.[123] It is a cell that is totally potent; hence has the capacity for developing into a complete organism, within a suitable environment, or, alternatively, undergoing meiosis with the consequent production of genetically unique gametogenous cells that upon division commence the production of trophoblast or its phylogenetic homologue.

Let us examine briefly the specific organizer effect of carcinogens in the differentiation of diploid totipotent cells in the lower organisms. In the Coelenterate *Obelia geniculata* the sexual generation embryos or medusae arise through the differentiation of the embryo-competent or diploid totipotent cells in the asexual generation hydranth. Hammett & Reimann[124, 125] observed that the addition of either 20-methylcholanthrene or 1, 2, 5, 6-dibenzanthracene to the aquaria of Obelia exerted such an organizer effect on the diploid totipotent cells of the hydranth colony as to increase the production of the sexual generation medusae by about 40%.

Methylcholanthrene has also been found to stimulate the multiplication of *Escherichia coli*[126] and to enhance both the regeneration of cut segments and the reproduction of whole animals of planaria[127] and to increase the proliferation of yeast cells.[128] Reproduction of the entire animal involves simple or direct differentiation of the diploid totipotent cell *without prior meiosis*; hence, no trophoblast or its phylogenetic analogue is produced and the resulting tissue is of an unchanged genetic composition.

Reimann[129] was able to induce the regeneration of claws in crustaceans through the application of steroid carcinogens, and Breedis[130] induced accessory limbs in salamanders with mixtures containing carcinogens. Waddington & Schmidt[131] described the induction of a twin embryo in the chick blastoderm through the implantation of an organizer.

The supernumerary planaria, medusae, and chick embryos were the result of the direct differentiation of diploid totipotent cells. The less extensive regenerative phenomena involving the inductions of accessory limbs or the regeneration of claws were the result of the differentiation of highly undifferentiated but not totipotent diploid cells. We can not review here the recapitulatory significance of the extragonadal occurrence

of diploid totipotent cells in the higher animals, but when these diploid totipotent cells exist in the canalization of the gonads or extra-genitally throughout the soma, specific organizer stimuli will induce them to differentiate *through meiosis*. Hearne[132] observed, for example, that 0.005 mg. of methylcholanthrene per c.c. of culture medium induced some of the cells in an *in vitro* preparation of mouse fibroblasts to undergo the chiasma formation of meiosis. Von Moellendorff[133] observed the same phenomena with estrone and benzpyrene.

Since the fibroblasts comprise the most primitive or undifferentiated multipotent cells of the soma, it is not surprising that a few totally undifferentiated or diploid totipotent cells should occur with them. Only the diploid totipotent cells are competent for meiosis, through the action of an organizer stimulus typified by estrogen. A single cell division separates the resulting gametogenous cell from trophoblast, and the single alternative to such division of the gametogenous cell with the inescapable production of trophoblast is death.

Cancer Is Not Embryonic

The fibroblast is correctly described as one of the most primitive *somatic* cells in the life-cycle. *The trophoblast cell is the most primitive cell in the life-cycle, but the trophoblast cell is neither somatic nor embryonic*, and never normally comprises a part of the definitive embryo or the post-natal individual. It exists in antithesis to all cells of the definitive embryo or the post-natal individual. *The trophoblast cell is not formed by the definitive embryo, does not form the embryo, and may persist in the absence of the embryo.*

Cancer is not embryonic. The more primitive a true embryonic cell is the more readily it conforms to the morphogenetic pattern or individuation field of the tissue in which it occurs or into which it is transplanted[134]. Needham[135] has aptly characterized cancer as "an escape from the individuation field." In the light of the unitarian thesis, this escape specifically involves the meiosis of a diploid totipotent cell and the subsequent presentation of ectopic trophoblast. This is of necessity "an escape from the individuation field" of the soma, since trophoblast is foreign and fiercely antithetic to that field.

It is to be emphasized that the trophoblastic or unitarian thesis not be confused with the Remak-Cohnheim theory, or its various modifications, based on the doctrine of "embryonic rests" or "shunted germs." The notion of "misplaced embryonic tissue" has been destroyed by the evidence of experimental embryology, and the fallacious Remak-Cohnheim hypothesis should at long last be decently interred.

The Life-Cycle. The trophoblastic or unitarian thesis of cancer is implicit in an accurate comprehension of the nature of the animal life-cycle, which comprises two fundamental segments or generations: the trophoblastic or asexual generation or segment and the definitive embryonic, somatic or sexual generation or segment. These two segments exist in profound antithesis to each other. This is the *life-cycle of antithetic metagenesis*, in which the total product of gestation is described as the

conceptus and in which the latter is divided into the trophoblast or its phylogenetic homologue (asexual generation) and the embryo or soma (sexual or somatic generation). In the earlier and purely morphologic account of the life-cycle, the total product of gestation was indiscriminately designated as *embryonic*. Within such an erroneous concept of the life-cycle the nature of cancer is, and will remain, incomprehensible. The phenomenon of cancer becomes an inescapable corollary of the correct concept of the life-cycle—the life-cycle of antithetic metagenesis. Here cancer is seen as an expression of a specific cellular differentiation in response to an organizer stimulus. The erroneous concept of the life-cycle, the non-metagenetic life-cycle, can offer only the erroneous postulate of spontaneous generation to account for the origin of the cancer cell.

Cancer and the Failure of the Detoxification Mechanisms

The chief organs of the reticulo-endothelial system for the detoxification of estrogen and other steroids are the liver and spleen. Impairment of the detoxification mechanism can be experimentally induced or can arise spontaneously in any one of a combination of ways: 1) poisoning by hepatoxins, such as carbon tetrachloride, chloroform, the azo dyes, selenium, beryllium, arsenic, and the other heavy metals; 2) excess of carcinogenic and estrogenic steroids; 3) such organic compounds as cincophen and various biological toxins; 4) dietary deficiencies; and 5) parasitization and viral infections. All these factors, through impairing the hepatic detoxification of steroids, can contribute to a carcinogenic excess and persistence of estrogen and related compounds.

Failure in Hepatic Detoxification. The primary or active estrogen elaborated by the gonads is estradiol. This is converted by oxidation into the relatively inert estrone and estriol, which are excreted by the kidneys[136]. Under normal conditions, the endogenous estrogen is inactivated or detoxified with remarkable rapidity and completeness[137, 138, 139, 140]. Zondek injected 20,000 m.u. into infantile rats and found no active estrogen in the urine. Three hours later he killed and minced the rats; extracting the mince, plus the faeces and urine, he was able to detect only traces of active estrogen. Thirteen men and nine women were given repeated intravenous injections of natural estrogens in doses of 100 to 400 mg. in 200 c.c. normal saline; only negligible amounts of estrogen persisted in the blood after eight hours[141]. Although dog's blood does not inactivate estrogen *in vitro*, 1,000 r.u. of estrogen injected into such blood circulating in a heart-lung-liver preparation completely disappeared within 15 minutes.[142]

Heller[143] observed that slices of liver *in vitro* inactivate estrogen, and that this inactivation is prevented by cyanide. Other authors have observed a quantitative relationship between the degree of hepatic damage induced by such hepatoxins as carbon tetrachloride and the rise of active estrogen in the blood and urine.[144, 145] Pellets of estrogen implanted into the spleen exerted no effect on castrate rats with normal hepatic function.[146]

Such rats remained anestrous when maintained on a diet adequate in the B complex, but with a diet deficient in the B complex the rats went into a continuous estrus.[147] The administration of brewer's yeast restored the anestrous condition. The same sequence of phenomena was observed by utilizing an intrasplenic implant of ovarian tissue as the estrogen source.[148] Both in experimental animals[149, 150, 151] and in man[152, 153] cirrhosis of the liver is accompanied by a decrease in the detoxification of estrogen—and a consequent increase in active estrogen. Such cirrhosis in both man[154, 155] and animals[156, 157] is known to arise through either dietary inadequacies, through infections, or through hepatoxic chemicals.

The spleen as well as the liver and the reticulo-endothelial system as a whole are active in the detoxification of steroids. The author has confirmed the observation of others[158, 159, 160] on the effect of the trophoblastic steroids, and estrogen, chorionic gonadotrophin (indirectly acting) and the carcinogenic steroids in inducing a pronounced splenic hypertrophy. A similar hypertrophy has been reported in the spleen of tumor-bearing animals[161, 162, 163, 164, 165] and tar treatment caused splenic hypertrophy prior to the onset of malignancy. Administration of tar, dibenzanthracene, benzpyrene or methylcholanthrene produced a splenic hypertrophy reported to vary with the degree of carcinogen used.[166]

Depression of the activity of the reticulo-endothelial system comprising the liver, spleen and other tissues is reflected in a decreased ability of this system to remove particulate material from the blood and lymph. This depression may be demonstrated through the decreased ability of the reticulo-endothelial system to clear the blood and lymph of Congo Red.[167-173] Claude[174] reported that the toxic effect of 1, 2, 5, 6-dibenzanthracene in rabbits was such as to produce liver degeneration followed by cirrhosis. Csato, Wetzler-Ligeti & Wiesner[175] found that the same carcinogen produced a considerable depression in the reticulo-endothelial function in thirteen out of fourteen rabbits. Benzpyrene and methylcholanthrene,[176] as well as protracted irradiation,[177] had a similar effect in rabbits. Non-carcinogenic hydrocarbons (1, 2-benzanthracene, phenanthrene, anthracene) in general failed to depress the reticulo-endothelial system.[178]

Berenblum & Schoental[179] have shown that the carcinogenic hydrocarbons are converted in part in the animal body into phenolic derivatives. It is significant that the oxidized or otherwise detoxified derivatives of the carcinogenic hydrocarbons that are excreted in the urine are as non-carcinogenic when administered to mice[179, 180] as the detoxified estrogens of normal urine are non-estrogenic when administered to test animals. In other words, neither *detoxified* substance is capable of exerting an organizer effect on a diploid totipotent cell or any other cell. In view of the fact that the pro-carcinogenic estrogen molecule differs from the anti-carcinogenic testosterone molecule only in the position of a single hydrogen atom at a reactive site, the importance of the biochemistry of the steroids to carcinogenesis is obvious.

Hepatic Cancer. Carbon tetrachloride affords a useful tool for the

study of the pathogenesis of hepatic cirrhosis, hepatic cancer, and the failure of the detoxification mechanism. Edwards[181] observed that mice fed a solution of carbon tetrachloride in olive oil over a period of several months showed a high incidence of neoplasms of the liver.[182] Furlong, Krichesky & Glass[183] found that carbon tetrachloride increased the urinary excretion of undetoxified estrogen in guinea pigs 350 times. Female rats given 0.05 c.c. carbon tetrachloride showed a progressive uterine enlargement over a period of three days; ovariectomized rats used as a control showed no such reaction.[184] Spayed rats were given carbon tetrachloride. Twenty-four hours later these animals plus spayed controls were given 1.5 gamma active estrogen. Vaginal smears at the end of 48 hours showed estrogenic activity in 62.2% of the animals whose livers had been injured by carbon tetrachloride and in 19.5% of those with healthy livers.[185]

Glass, Edmundson & Soll[186] examined fourteen men with cirrhosis of the liver and found such evidence of excessive estrogen activity as atrophy of the testes in all and gynecomastia in eight. Jacobs[187] described gynecomastia in men following severe starvation, which resulted in the inability of the liver to detoxify estrogen. A diet low in protein and high in lard produced massive hepatic necrosis in rats.[188] Jailer & Seaman[189] found that rats on a vitamin B complex deficient diet could still inactivate estrogen if they were fed a diet containing 50% casein, but that a diet of 5-to-15% casein under the same conditions caused a loss of the ability to detoxify estrogens.

Basu & Ray[190] found that in rats with livers severely damaged by carbon tetrachloride, the addition of vitamin B-1 to the diet would increase the excretion of glycuronic acid in response to a standard quantity of chloral hydrate. Vitamin B-1 forms the prosthetic group of cozymase, which is part of the hepatic estrogen detoxifying system.[191] Pellets of estrogen implanted into the spleen of spayed rats left them anestrous, but on a vitamin B-1 deficient diet the hepatic detoxification of estrogen failed sufficiently to cause such animals to go into continuous estrus.[192]

The direct role of estrogens in the induction of hepatic cancers is indicated further by Andervont, Grady & Edwards[193] who found that castration of female mice reduces their susceptibility to hepatic cancer induced by azo dyes. Castration of male mice was found to increase the incidence of such cancers. However, if the castrated male mice were given testosterone, the incidence of hepatic cancer dropped to that of the castrate females. And if the intact females were given testosterone, their incidence of hepatic cancer decreased to that of the intact males.[194] The incidence of azo dye-induced hepatic cancers was depressed by chorionic gonadotrophin.[195] Caloric restriction was also found to depress the incidence of hepatic cancers in mice.[196]

It may be recalled that the incidence of spontaneous mammary cancer in certain strains of mice is inhibited by: 1) ovariectomy, 2) the administration of testosterone, 3) caloric restriction, and 4) administration of chorionic gonadotrophin; and that 5) the administration of estrogen or 6) the im-

plantation of ovarian tissue into spayed females (or 7) into castrated males of the same strain results in an incidence of mammary cancer normal for the intact females. According to the unitarian or trophoblastic thesis, the origin of these mammary cancers and hepatic growths involves the organizer effect of estrogen on the competent cell—the diploid totipotent cell.

We have observed that there are only two classes of true or directly acting carcinogens:

I. Normally occurring estrogens

II. Substances that duplicate the morphogenetic action of normally occurring estrogens.

In Class III we found (cf. p. 31) the factors which inhibit the detoxification of normally occurring estrogens—or that of substances that specifically duplicate the morphogenetic action of normally occurring estrogens.

The azo dyes, carbon tetrachloride, chloroform, beryllium, selenium, arsenic, similar compounds and elements, dietary inadequacies, and the metazoan parasites exert their carcinogenic effect in the induction of hepatomas and other cancers through the impairment of the liver and associated reticulo-endothelial tissues in the detoxification of estrogen or steroids duplicating the morphogenetic effect of estrogen. Shear, Stewart & Seligman[197] found that the direct implantation of carcinogenic polycyclic hydrocarbons into the normal liver showed this organ to be the most resistant of all to carcinogenesis.

While both carbon tetrachloride and chloroform will induce hepatic cancer in mice, carbon tetrachloride is eight times more necrotizing to the liver than chloroform, and it is also about eight times as carcinogenic. It is similarly more effective in inducing hepatic cirrhosis. Eggel[198] found cirrhosis of the liver coexisting with 85% of the hepatic carcinomas in man. Stewart[199] found a coexistence of 89%. In both man and animals hepatic cirrhosis is associated with a loss of the detoxifying ability of the liver.

Primary cancer of the liver is relatively rare in those living on the reasonably adequate dietary of the North American continent and Europe. Berman,[200] however, reported a high incidence of liver carcinoma among South African natives. In the Witwatersrand gold mines primary carcinoma of the liver accounted for 90.5% cases of cancer amongst the Bantus recruited from the native territories or from Portuguese East Africa. It is striking, indeed, that cirrhosis of the liver is found in four out of five autopsies performed on male Bantus at the Johannesburg General Hospital.[201]

The poverty of these natives forces them to live upon the cheapest carbohydrate—corn, maize or mealie meal—supplemented by fermented cow's milk. When the same diet was fed to rats for two years, a frank cirrhosis of the liver developed in 20% of them but no cancer occurred. The absence of cancer from such feedings is not surprising, since Gyorgy, Polling & Goldblatt[202] reported cirrhosis but no tumors in rats fed on a synthetic diet containing azo dyes. However, in 53 rats with selenium-

induced hepatic cirrhosis, 11 developed hepatic cancer within 18 to 24 months. Though cirrhosis frequently developed after three months, no cancers appeared until the passage of 18 months.

Hepatic Cirrhosis. *All* of the agents known to produce hepatomas are also capable of producing hepatic cirrhosis. The carcinogenicity of arsenic, for example, is a subject that has stimulated much enquiry. The liver is one of the chief storage places for arsenic in the body.[203-206] Arsenical cirrhosis of the liver has been reported in man by a number of workers,[207-16] as has the experimental induction of arsenical hepatic cirrhosis in animals.[217-20] Despite the fact that arsenic and the azo dyes are much more effective in producing hepatic cirrhosis than are the carcinogenic polycyclic hydrocarbons, their carcinogenicity is not comparable in degree to the true or direct-acting carcinogens.

The repeated cutaneous application of tar for the production of skin cancer in rabbits will often induce hepatic cirrhosis,[221-26] as will the injection of 1, 2, 5, 6-dibenzanthracene. Similar effects have been observed for benzpyrene and methylcholanthrene. Since these compounds impair the ability of the liver to detoxify estrogen, they result in an increase of active estrogen. This carcinogenetically additive effect of active estrogen is further augmented by the associated loss in the ability of the liver to detoxify the exogenous carcinogens themselves.

Hepatic Parasites and Cancer

Opisthorchids felineus,[227] *Schistosoma haematobium,*[228] *mansoni,*[229] and *japonicum*[230] are among the parasites that have been identified with a high incidence of primary cancer of the liver in man. All of these parasites are very active in producing hepatic cirrhosis in man. In studying 36 primary liver carcinomas among African natives Pirie[231] found the coexistence of cirrhosis in 31 cases, ten of which could be tracted to *S. haematobium.*

According to the unitarian or trophoblastic thesis, the causal sequence of these tumors is roughly as follows: parasitization of the liver, necrosis, fibrosis, cirrhosis, consequent loss of steroid detoxifying capacity, estrogen and other steroid excess, localization of steroids by inflammatory area, meiosis of diploid totipotent cell, division of resultant cell, and ectopic presentation of trophoblast in the liver—and concomitant to it all, a depression in the host of factors antithetic to trophoblast.

Some workers have suggested that the parasites themselves release carcinogenic steroids. While such a possibility is supportable by the trophoblastic thesis, it lacks experimental demonstration. The suggestion by Borrel that these parasites all carry carcinogenic viruses may, of course, be dismissed as fanciful.

Focal Detoxification of Steroids. Since elements of the reticuloendothelial system are ubiquitous, it is not surprising to find most tissue equipped for the local detoxification of steroids and associated substances. One of the few systematic pieces of work done on this subject is that on the beta-glycuronidase problem by Fishman and his associates.

Wherever one looks in the field of oncology, he will meet the consequences of the fact that the constant malignant component (cancer cell) of the composite tissue of cancer is trophoblast. The beta-glycuronidase problem is no exception to this generalization. It is now well established that trophoblast produces both a specific gonadotrophin and considerable quantities of estrogenic steroids.[231, 232] An elucidation of their position in the life-cycle may be found in other papers by the author and his associates.[233, 234] Because the cancer cell is trophoblastic and because the trophoblast produces estrogenic steroids, it is not surprising that many workers[235-39] have found an increased content of estrogenic steroids in cancer tissue. Fishman and his coworkers have identified a powerful beta-glycuronidase activity associated with the metabolism of estrogen in the uterus. It is, therefore, significant that these workers[240-43] have found an increase of 100 to 3,000 times the normal level of beta-glycuronidase in primary cancer of the breast, stomach, esophagus and other tissues, as well as in their metastases. Fishman correctly pointed out that this activity "must" be due to an increased level of estrogen in such tissue.

Incidentally, these extensive data on the increased concentration of estrogen and beta-glycuronidase in malignant tissues are further evidential of the unitarian nature of cancer. The trophoblastic nature of cancer is an inescapable corollary of its unitarian nature, not only on the basis of the occurrence of trophoblastic estrogen and an associated increase in beta-glycuronidase in all exhibitions of cancer, but more conclusively in the fact that primary uterine chorionepithelioma as well as testicular and extra-genital chorionepithelioma comprise in their frank exhibition of trophoblast cells the most malignant exhibitions of cancer possible.

It is a commonplace in the experimental induction of cancer that the inductive agent does not persist in the tumor after its formation. The fact that estrogen is found in cancer tissue is readily explicable in terms of the normal role of the trophoblast in the life-cycle. In the course of normal gestation the syncytial trophoblast is the main source of the steroidal sex hormones that maintain the integrity of the gestational uterus. In fact, bilateral ovariectomy of the human female after the first week of conception fails to result in abortion or an appreciable decrease in urinary pregnandiol because of the steroid production of the syncytial trophoblast.[244]

If cancer is anything, it is a phenomenon involving the growth of primitive cells. That it should involve the most primitive cells in the life-cycle—rather than spontaneously created cells—is not surprising.

Roentgen Rays and Ultraviolet Radiation

Total irradiation of mice of certain strains leads to the development of granulosa-cell tumors of the ovary.[244, 245] These tumors are productive of large quantities of estrogen and are significantly related to an elevated incidence of mammary cancer in mice and uterine cancer in man. Total irradiation also leads to an increased incidence of leukemia in susceptible

mice.[246, 247] Both mammary tumors and leukemia in mice have 1) been experimentally induced by the injection of estrogen; and have 2) been prevented through ovariectomy; 3) through the injection of testosterone; or through caloric restriction. For example, Murphy[248] observed, in a study of the RI strain of mice, that the incidence of leukemia in intact females was 88% and in intact males, 54%. In castrated females the incidence was 90% and in castrated males, 97%. The administration of testosterone reduced the incidence in ovariectomized females to 58%. The role of estrogen in the elevated incidence of leukemia is clear.

The induction of granulosa-cell tumors in response to the radiation-induced outpouring of estrogen-evoking gonadotrophin from the pituitary is an extreme expression of the capacity of radiation to induce a hyperestrogenism—as the following experiments demonstrate. Female rats were maintained in parabiotic union with normal males; if in this condition the male rats were sterilized by x-rays, the female partners arrived at a state of constant estrus.[249] Witschi, Levine & Hill[250] sterilized male rats by exposure of the scrotum to x-rays. One month later these rats in parabiosis with normal females kept the latter in a condition of constant estrus. Johnson[251] confirmed these findings on rats, using x-rays in some instances and radium in others. Martins[252] further specifically demonstrated that x-ray sterilization so affected the pituitary that it produced a continuous supply of estrogen-evoking FRH and little or no testosterone—or progesterone-evoking LH. The pituitary changes resembled those of castration.

Kirschbaum[253] has recently demonstrated a synergistic action between estrogenic hormones and roentgen rays in the induction of lymphosarcoma in mice. Since lymphosarcoma has been induced in mice by estrogen injections, and since radiation increases the titer of endogenous estrogen, it is not surprising that the effect of radiation and estrogen injections is additive in the induction of lymphosarcoma in mice. Zurhele[254] reported that irradiation, likewise tar treatment, induced irreversible changes in the mesenchyme prior to tumor induction. Protracted roentgen irradiation duplicated the effect of methylcholanthrene and benzpyrene in profoundly depressing the reticulo-endothelial function in 13 out of 14 rabbits.[255]

The long latency period of roentgen- and radium-induced cancer indicates that carcinogenic effect is not a direct one. Radiation is known to induce genetic mutations in diploid totipotent cells, that is true. But *no evidence whatever exists for the idea that the carcinogenic effect of radiation is due to the mutation of any cell.* On the other hand, the experimental evidence is conclusive that radiation can prove carcinogenic through elevating the estrogen output of the organism.

Bone Cancers. The radium salts belong to the same chemical grouping as calcium; for this reason the radium salts tend to accumulate in the bones following ingestion (or inhalation). Administration of estrogen increased the incidence of bone tumors in male mice of a strain in which females showed a susceptibility to spontaneous bone tumors.[256] The intravenous injection of radium salts produced osteogenic sarcoma in rabbits[257] and in rats.[258] Bone is a natural target-organ for estrogen and the vitamin D

steroids, and estrogen injections in mice cause the replacement of bone marrow by osseous tissue.[259] The localization of radium salts in the bone provides: 1) a focal inflammation capable of concentrating estrogen and other substances (cf. p. 54); 2) a substance capable of inducing hyperestrogenism in the body; and 3) a target vulnerable to estrogen because it comprises not only a natural target-organ for estrogen but a localizing focus for estrogen as well as an estrogen-evoking factor in the target. It would be difficult, indeed, to understand how a diploid totipotent cell in such an area could escape meiotic induction with consequent trophoblast formation.

The association of leukemia in man with exposure to radium and roentgen irradiation is indicated by the fact that the incidence of leukemia among radiologists is 17 times higher than among the general population.[260, 261] While the incidence of spontaneous leukemia is greater in female mice than in male mice, it is greater in men than in women. We are inclined to account for this by the fact that 1) the gonads in the human male are unusually vulnerable anatomically and 2) the human male is exposed to greater occupational hazards.

Ultra-Violet Radiation and Photosensitizing Substances. The absorption of ultra-violet radiation is augmented by such photosensitizing substances as the porphyrins. Figge[262] found that the injection of porphyrins decreased by 50% the latent period for the induction of methylcholanthrene cancer in mice. He also observed, significantly enough, that a dose of estrone (0.5 gamma) sufficient to induce estrus in about 50% of the injected rats would induce estrus in practically 100% of the animals if they were first sensitized by porphyrin injections. A consideration of the mechanism by which an endogenous excess of porphyrin may be produced is beyond the scope of this paper; however, any endogenously occurring substance that will double the biological activity of estrogen is certainly relevant to the cancer problem.

Estrogen is the only normally occurring substance in the higher animals for which carcinogenic properties have been conclusively established. Carcinogenicity of estrogen is more universal, in terms of susceptible animals and the diversity of malignant exhibitions induced, than that of any other substance. The *only* cell in the life-cycle productive of trophoblast is the diploid totipotent cell; the only mechanism of production, meiosis; and the only normally occurring evocator, estrogen. The trophoblast is the *only normally occurring cell in the life-cycle* for which no ascertainable intrinsic change—morphological, endocrinological, physiological—has ever been found between its normal and its malignant exhibition. The trophoblast cell is the *only* cell that has never been observed in the male or, outside of the canalization of pregnancy, in the female except as cancer.

Localization of Carcinogens

Failure in the normal detoxifying capacity of the liver and other parts of the reticulo-endothelial system results in the abnormal persistence of active estrogen and, when present, exogenous carcinogens. This failure is often associated with, and thereby reinforced by, an increase in the pro-

duction of estrogen. A high and abnormally persistent concentration of estrogen reciprocally inhibits the production and secretion of the anterior pituitary hormones, some of which—according to the trophoblastic or unitarian thesis—are necessary in mediating the resistance of the host to trophoblast.

The abnormally high titer of estrogen presents the organizer by which carcinogenesis may be achieved when the apposition of such organizer and competent cell occurs. Since the competent cell in carcinogenesis is always the diploid totipotent cell, the susceptibility of this cell to organizer action is a constant. The variable involved, then, is *the focal concentration of effective organizer*. The important determiners of this are as follows: 1) the physiological concentration of estrogen in target organs—mammary glands, cervix, uterus, testes, prostate, lymphoid tissue and bone; 2) direct contact with, or inhalation or ingestion of, exogenous carcinogenic compounds; and 3) a combination of (1) and (2).

Brunelli[263] observed that estrogen injected intravenously concentrates in inflamed tissues. Carcinogenic hydrocarbons do likewise. Menkin[264] has studied this phenomenon comprehensively and has shown that concentration of steroids and other material at an inflammatory site is due not only to an increase in blood-supply but also to the occlusion of the afferent capillaries with fibrin plugs.

The susceptibility of a tissue to a focally effective concentration of organizer (carcinogen) is not enough to induce carcinogenesis. There must be available an adequate supply of *undetoxified* organizer to implement this susceptibility. This necessitates a relative or absolute failure in the steroid detoxification mechanism. A localization of an effective concentration of estrogen will cause the diploid totipotent cell to undergo meiosis with resultant production of trophoblast but unless the resultant trophoblast persists and is not destroyed, as a result of humorally mediated factors antithetic to it, cancer does not occur.

The specific nature of the mechanism by which trophoblastic growth is controlled will be reviewed in Part II of this paper. We have traced only a few of the pathways by which the carcinogenic effect may be mediated; and of these few pathways we have considered only a few of the multiple possibilities for their interrelations.

In conclusion of Part I, let us reduce the phenomena of cancer to their simplest denominators: 1) cancer is the expression of the spatially or temporally anomalous occurrence or persistence of trophoblast*; 2) cancer arises through the meiosis of a diploid totipotent cell and the division of the consequent gametogenous cell to trophoblast; and 3) the organizer chemical "normally" involved is estrogen.

*Only in primary uterine chorionepithelioma and in the chorionepitheliomas of tubal or ovarian pregnancies is the trophoblast sexually induced. But in all exhibitions of cancer the malignant cell is genetically unique from the cells of the host, but not even this factor is indispensable. In uterine and tubal pregnancies so-called "blood-moles" sometimes develop in which the trophoblast destroys the genetically identical cells of the contiguous embryo (265, 266). Reduced, then, to its simplest denominator, cancer is the expression of the antithesis of *any* trophoblast against non-trophoblast.

END OF PART I—BIBLIOGRAPHY WILL BE PRINTED IN A SUBSEQUENT ISSUE.

GENERAL PRACTICE CLINICS

VOL. 8 NO. 3 MARCH 1951

Obstruction of the Lower Portion of the Urinary Tract in Infants and Children. *Meredith Campbell, New York, N. Y.* J. Internat. Coll. Surgeons. 14:294–99, Sept. 1950.

Congenital obstructive lesions of the urethra are relatively common, particularly stenosis of the external urethral meatus. Other lower urinary tract obstructions in infants and children include congenital stricture deeper in the urethra, traumatic urethral stricture, congenital vavular obstruction of the prostatic urethra, congenital hypertrophy of the verumontanum, congenital contracture of the vesical outlet, neuromuscular vesical disease and, rarely, ureterocele, trigonal curtain obstruction and sarcoma of the prostate. All of these lesions when they obstruct cause essentially the same symptomatic picture, chiefly urinary frequency and difficulty often complicated by infection and, if unrelieved, terminal uremia.

The diagnosis is readily made by complete urologic examination. Urethral dilatation is usually adequate treatment of urethral strictures, while the described lesions of the prostatic urethra and at the vesical outlet readily respond to transurethral resection.

Only by clinical alertness to the frequency and potential extreme gravity of these conditions and with prompt diagnosis and treatment, will these young children be afforded opportunity and hope of cure, and the preservation of a more or less normally functioning upper urinary tract. The clinical therapeutic problems are comparable to those of prostatic obstruction in adults.

Diverticula of the Female Urethra. *Lawrence R. Wharton and Walter Kearns, Baltimore, Md.* J. Urol. 63:1063–76, June 1950.

This article reports 30 cases of urethral diverticula in women. In four of these cases the opening of the diverticulum into the urethra was in the anterior third, in nine cases in the middle third and in eight cases in the posterior third; in all, the opening was on the vaginal half of the

urethra. In one case a single diverticulum had twin openings; in another case there were two separate diverticula in the urethra, as shown by the X-ray findings and proved at operation. Associated infection of the urinary tract was present as a rule, but invoked only the urethra and the bladder in all but two cases. Calculi were present in the diverticula in ten cases, sometimes a single stone, in other cases multiple stones. In all these cases there was infection and pyuria, and in one case a stone in the kidney. Urethrovaginal fistula, resulting from rupture of the diverticulum into the vagina was not observed in this series, but has been reported by others. A small urethral diverticulum that is not infected may not cause symptoms. The usual symptoms were those of a chronic recurring cystitis that was resistant to the usual methods of treatment. In some cases the patient noticed a vaginal mass, usually in association with dyspareunia, but as a rule the vaginal mass was discovered by the examining physician. The presence of this vaginal mass from which pus could be expressed into the urethra was the commonest pathognomonic sign in the series reported by which diagnosis could be established. The demonstration of the opening of the diverticulum and its visualization by X-ray were also of value in diagnosis.

In the 30 cases reported surgical excision of the diverticulum was done in 17 cases, and incision and drainage in five cases. In the other cases conservative methods were used, such as urethral dilatation or cauterization by electro-cautery or silver nitrate. The best results were obtained in the 17 cases in which excision of the diverticulum was done; in one of these cases arthritis which had been present was relieved when the recurring cystitis cleared up after the operation. In two of these cases, however, a urethrovaginal fistula developed, which in one case caused no inconvenience and in the other was cured by urethral dilatation. In cases in which the diverticulum is friable or closely adherent to the urethral sphincter or the bladder, radical dissection is not indicated, or if the diverticulum is merely an abscess sac, some of the sac can be left, and cauterization employed to destroy the lining membrane.

In addition to the 30 cases in which the presence of a urethral diverticulum was definitely demonstrated, there were 14 cases of suburethral cysts and eight cases of suburethral abscess in women observed during the same period, which produce much the same symptoms as urethral diverticula, and may be closely allied to them. It should be recognized that the female urethra may be of importance in causing or perpetuating disease in the urinary tract. 7 figures. 18 references.

The Female Urethra: A Histologic Study as an Aid in Urethral Surgery. *J. V. Ricci, J. R. Lisa and C. H. Thom, New York, N. Y.* Am. J. Surg. 79:499–505, April 1950.

A histological study of the female urethra was made in 21 specimens

from the fetus, newborn infants and adults. The essential structure of the female urethra was found to be the same at all ages; there were no changes except the atrophy that occurs with advancing age. These studies show that the female urethra has three layers: an inner layer of stratified squamous epithelium; a layer of substantia propria which in the upper two thirds consists of fibrous connective tissue with numerous fine elastic fibers, but in the lower third becomes a thickened fibrous tissue; the other layer, which is muscle. The upper third of this muscle layer is a continuation of the musculature of the bladder. Skene's ducts and para-urethral glands are present at the external orifice of the ureter, and a few glands are occasionally present at the internal orifice. No lymphatic glands were found in the urethra. 6 figures.

Memory Studies in Electric Convulsion Therapy. *Moyra Williams, Chichester, England.* J. Neurol. Neurosurg. Psychiat. 13:30-35, Feb. 1950.

An attempt was made to study alterations of perception at the same time as those of memory in post-ECT amnesic states. Three sets of pictures were standardized and used in the investigation. The first picture in each was a circular ink-blot while the last was a silhouette study of an animal, the intermediary pictures representing various stages between the two. The subjects studied were 19 unselected patients undergoing a course of ECT for depressive states. They were interviewed some time during the day before treatment, again during the confusional period immediately after treatment, and again some hours later. During each interview the subjects were shown a set of pictures whose principle was explained to them, and asked to guess at each stage what animal the set would turn into. The sets were taken in turn. The set shown to a subject before treatment was shown to him again immediately after it, together with another set. This second set and the last one were shown again at the third interview.

It was discovered that despite lack of recall or recognition, the set of pictures seen before treatment was recognized by each subject in the confusional period more easily than the new set. Furthermore, if the new set was shown a second time during the confusional period, it was recognized earlier at the second presentation, although the patients denied having seen it before.

Comparison of a subject's responses made to a set of pictures on two different occasions showed that verbal responses and constructions made to one of the earlier pictures in the set were usually repeated when the set was seen again but at an earlier point in the series. This was regarded as suggesting that what appeared to be a recognition of the stimulus might be better interpreted as facilitation of a pattern of verbalization. 14 references. 6 tables—*Author's abstract.*

Suicide. *Carl L. Kline, Milwaukee, Wisc.* Wisconsin M. J. 49:111–13, Dec. 1950.

Some general statistical facts of interest about suicide are presented. Many misconceptions about suicide are mentioned and discussed briefly. It is important to recognize that many of the reasons given for specific instances of suicide are not actually the cause of the tragedy.

Some important considerations in judging suicidal trends in an individual patient were discovered. These considerations included the evaluation of depression as a symptom and of elation as a symptom. Oral-dependency is discussed in the same connection, as were several other general factors.

The paper concludes with a brief discussion on the management of the suicidal patient. It is emphasized that by working together the medical man and the psychiatrist can rehabilitate many depressed patients and avert a number of significant tragedies.—*Author's abstract.*

Investigation of Autonomic Responses in Psychopathic Personalities. *C. J. Ruilmann* and *M. J. Gulo, Memphis Tennessee.* South. M. J. 43: 953–56, Nov. 1950.

Using the Keeler polygraph, psychological stimuli applied were aimed at exploring inter-personal relationships. In this setting, those designated as psychopaths appeared to show much less uneasiness and apprehensiveness about such relationships even though their long-term histories had been marked by many failures in this regard. The failure to respond in terms of activity of the galvanic skin reflex was most marked in those patients who had experienced very early difficulty in the beginnings of inter-personal relationships with the parents. In those individuals in whom no dynamic psychological factors could be found to be related to the personality defect the reactivity was much more marked but seemed to be indiscriminate and sometimes inappropriate. Because of the great amount of time involved in studying each case, we have not as yet amassed a sufficient number in each category to be able to give incontrovertible statistical data. The technic, however, seems sufficiently worth while to merit further study.

Many other authors have suggested that much so-called psychopathic behavior is based on the individual's inability to form meaningful inter-personal relationships with those around him. In this belief, we concur and we suggest in addition that this failure is in fact, a deficit in personality structure and probably does not represent repression or suppression of these conflicts to relatively unconscious levels since in other patient groups where such processes had played a part, a powerful anxiety type response could be provoked whenever the psychological stimuli touched on the relatively unconscious conflictual material.

We believe this study offers objective verification of the clinical impression that the character defect in the so-called psychopath is indeed a fundamental one and, further, that the technic described has value as a diagnostic implement. 23 references. 5 figures.—*Author's abstract.*

BOOK REVIEWS

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY, published by Merck & Co., Rahway, N. J., 1950, Price $4.50.

This new edition is more inclusive than all previous issues, emphasis, of course, being placed upon diagnosis and treatment. It was edited by an editorial board who consulted over a hundred clinicians in order to make the work accurate authentic and up-to-date. Part I is devoted to diseases and major symptoms; Part II presents routine, clinical and laboratory procedures. The chapters are arranged alphabetically rather than anatomically. Each disease entity presents the usual survey of the disease patterns, its symptoms and signs, diagnosis and therapeutic procedures. A series of useful prescriptions are given at the end of each group of related disorders. In the attempt to condense information on the mechanism and management of disease, there is an occasional inadequacy or inaccuracy of statement. For example, in idiopathic thrombocytopenic purpura, the statement is made that examination of the bone marrow reveals increased megakaryocytes but little platelet formation. Actually, there are abundant platelets that are destroyed by a toxic factor emanating from the spleen. To indicate that there is a maturation arrest of megakaryocytes is erroneous because in such cases splenectomy did not prove to be effective therapy. The advice given that splenectomy, performed in all forms of thrombocytopenic purpura, is effective therapy is not consistent with current experience. It is more favorable to resort to splenectomy in the quiescent and, preferably during the chronic stage of the disease. There is further inaccuracy in the statement that splenectomy is effective in most cases. Actually, many purpuras may recur in spite of therapeutic splenectomy. Another failing of a condensed manual is to group all forms of treatment at the end of the chapters. In the control of hemorrhagic disease, the forms of therapy given would not necessarily apply to each of the diseases. There are some worthy highlights well presented such as antibiotic therapy, crystalline vitamin B_{12}, Cortisone and A C T H. As a whole the handbook is a veritable mine of ready condensed information on all aspects of medical care and is indispensable in everyday practice.

TEXTBOOK OF ENDOCRINOLOGY, edited by Robert H. Williams, M.D., published by W. B. Saunders Company, Philadelphia, 1950.

This monograph embraces all aspects of the endocrinopathies. There is a thorough evaluation of the underlying principles of hormone secretions and their interrelationship. So many hormones have been made available in pill-form and so much has been learned about the manner in which they influence propagation, growth, maturation that their application to glandular disorders is better understood. Indeed, considerable attention has recently been turned to the role of endocrines in heart failure, hypertension, gerontology, immunology, hematology and in the therapy of neoplasms and collagen diseases. The author approaches these problems from the standpoint of recent chemical and physiologic advances. The

initial chapters are devoted to the laws of endocrinology and the subsequent chapters to the physiology and pathology of all the glands. Each chapter is treated with great thoroughness. For example, diabetes mellitus is discussed from the standpoint of the mechanism of the underlying metabolism. Parathyroid disorders are presented in terms of classification of bone diseases and calcium and phosphorus metabolism. There is a complete discussion of the psychodynamic aspects of endocrinology. Finally, there are laboratory procedures indispensable in diagnosis and treatment. The book is well written, unusually well correlated, beautifully illustrated and readily amenable to everyday reference.

THERAPEUTICS IN INTERNAL MEDICINE, edited by Franklin A. Kyser, M.D., published by Thomas Nelson & Sons, 1950.

The basic plan of this book includes tested therapeutic measures for the effective treatment of medical disease. Each subject is covered adequately with underlying physiologic principles. Each chapter is written by a clinician with particular experience in his field. Every phase of medicine is covered, except surgical. After a preliminary introduction evaluating the nature of disease, each author presents the therapeutic armamentarium available for the proper management of the disease. The source of therapy is given in references at the end of each chapter. The organization of the book makes it a ready reference for the practitioner. Some of the chapters give relatively scant information on the actual therapeutic procedures. For example, a practitioner would be unable to treat a patient with thrombocytopenic purpura because of the generalities implied in the procedures. On the whole the book is invaluable for everyday treatment of common disorders. It is well written, clearly diagramed and highly summarized for quick reference. Each chapter gives a terse summary of the relative merits of the various drugs that may be used in treatment. That is invaluable in view of the great confusion that exists in determining the order of merit of any particular treatment.

MANUAL OF ALLERGY FOR THE PATIENT, by Florence Eastty Sammis, M.Sc., M.D., published by Edwards Brothers, Inc., 1950.

The progress of modern science has made medicine more complicated not only for the physician, but also for the patient. When the doctor's instructions consisted of: "Take one teaspoonful three times a day," faith and patience were the principal attributes of a good patient.

More insight is necessary in the treatment of allergic diseases. If skin tests indicate a high degree of allergy to karaya gum, a vegetable substance with dozens of uses in industry, pharmacy and commercial preparation of foods, both doctor and patient may find it difficult to decide whether the patient has enough contact with it to logically account for his symptoms.

Despite endless questioning by the physician, only the patient knows

the details of his daily activities, environment and diet. When a diet without milk, eggs and wheat is prescribed, the patient may ask the doctor many difficult questions about cooking and planning meals. The sufferer from ragweed hay fever may plan his vacation to avoid contact with this weed only to learn that resort advertisements are not always botanically correct.

Dr. Sammis has presented in this book much of the varied information that will enable the allergic patient to cooperate intelligently with his physician, and save the latter hours of tedious explanations. No encouragement is offered for self diagnosis and self treatment; the purpose is purely to help the allergic individual to furnish pertinent information and carry out professional advice.

Since the book is designed for instruction of allergic patients rather than entertainment of pseudo-scientific readers, one will find little space devoted to the psychosomatic factors which occasionally contribute to allergic symptoms. These aspects, which have been overemphasized by more sensational writers, are wisely left to be handled by the physician in the individual case, so the reader is not led into the mazes of self-analysis.

Through The Menstrual Years of Life-
THE frequency with which the menstrual life of so many women is marred by functional aberrations that pass the borderline of physiologic limits, emphasizes the importance of an effective uterine tonic and regulator in the practicing physician's armamentarium.
In ERGOAPIOL (Smith) with SAVIN the action of all the alkaloids of ergot (prepared by hydro-alcoholic extraction) is synergistically enhanced by the presence of apiol and oil of savin. Its sustained tonic action on the uterus provides welcome relief by helping to induce local hyperemia, stimulating smooth, rhythmic uterine contractions and serving as a potent hemostatic agent to control excessive bleeding.
May we send you a copy of the booklet "Menstrual Disorders", available with our compliments to physicians on request.
MARTIN H. SMITH COMPANY
150 LAFAYETTE STREET, NEW YORK 13, N. Y
INDICATIONS
Amenorrhea, dysmenorrhea, menorrhagia, metrorrhagia and in obstetrics.
DOSAGE
1-3 cap. 3-4 times daily.
SUPPLIED
In ethical pkgs. of 20 cap.
ERGOAPIOL (SMITH) with SAVIN
· · THE PREFERRED UTERINE TONIC · ·

a b c d
PANTHENOL
b_1
NIACINAMIDE
b_6

℞ TO SPEED CONVALESCENCE

THERA-VITA* 'WARNER'

with Synthetic Vitamin A

The multivitamin preparation of therapeutic proportions without fishy after-taste.

Prescribe THERA-VITA* 'Warner' to meet increased vitamin requirements and to facilitate recovery in viral or bacterial respiratory tract infections and debilitating disorders. Also for *intensive therapy* of vitamin deficiencies encountered in allergic disorders, pregnancy, postoperative convalescence, inadequate diet, hyperthyroidism, gastrointestinal disturbances, metabolic disorders.

DOSAGE: *One to three capsules daily as required.*

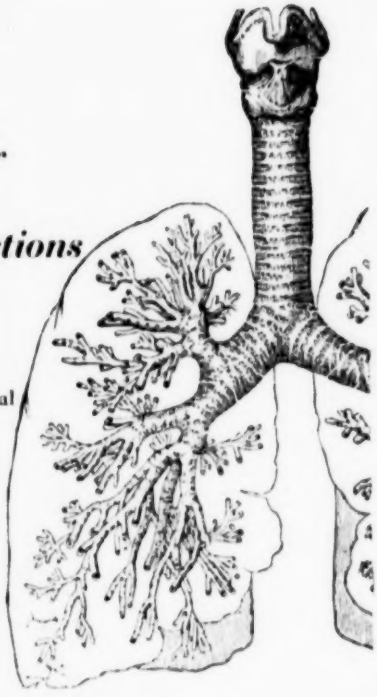
PACKAGE INFORMATION: THERA-VITA*, *Therapeutic Vitamin Capsules 'Warner,' are available in bottles of 25, 100, and 1000 capsules.*

WILLIAM R. WARNER
Division of Warner-Hudnut, Inc.
NEW YORK LOS ANGELES ST. LOUIS

*T. M. Reg. U. S. Pat. Off.

"prompt" response
"excellent" response
"...extremely effective"

in acute upper respiratory infections



Promptness of response to therapy is essential in these infections to accelerate the patient's recovery and prevent the spreading of infection. Acute laryngotracheal bronchitis (H. influenzae)[1], acute follicular tonsillitis (Str. pyogenes)[2], and streptococcic pharyngitis[3,4] are among the conditions in which uniformly favorable responses described as "excellent" and "prompt" have been obtained with this new antibiotic agent. In pharyngitis particularly, it has been noted that Terramycin "...given orally appears to be extremely effective."[5]

University Microfilms
313 N. First Street,
Ann Arbor, Michigan

CRYSTALLINE
Terramycin
HYDROCHLORIDE

The growing clinical literature continues to stress:

1. ***The broad-spectrum activity of Terramycin***
   against organisms of the bacterial and rickettsial as well as several protozoan groups.
2. ***The promptness of response to Terramycin***
   in acute and chronic conditions affecting a wide range of systems, organs and tissues.

Supplied:

250 mg. capsules, bottles of 16 and 100;
100 mg. capsules, bottles of 25 and 100;
50 mg. capsules, bottles of 25 and 100.

1. Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Ann. New York Acad. Sc. 53:440 (Sept. 15) 1950.
2. Herrell, W. E., Heilman, F. R., Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950.
3. Knight, V.: New York State M. J. 50:2173 (Sept. 15) 1950.
4. Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Ann. New York Acad. Sc. 53:433 (Sept. 15) 1950.
5. Schenck, H. P.: M. Clin. North America 34:1621 (Nov.) 1950.

Antibiotic Division **Pfizer** CHAS. PFIZER & CO., INC., *Brooklyn 6, N.Y.*

1941 A Decade of Progress in Antibiotic Therapy *1951*